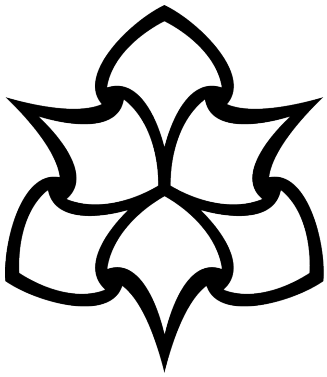

Integration of Patient Reported Outcomes in Pharmaceutical Drug Development For Prostate Cancer – Focus on the Patient

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Carl Stefan Holmstrom

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Department of Health Professions Faculty of Health, Psychology and Social Care
The Manchester Metropolitan University

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Abstract

Understanding, and adequately articulating how and what the patient feels and experiences during the progression of a disease and during drug treatment is an important aspect in a patient's life. Yet this articulation does not always get appropriate attention and thus the patient experience may not be fully understood by others. Nor is it fully explored in drug development programs due to the lack of focus on patient outcomes. Drug development has in the past primarily focused on meeting the regulatory approval of the new drug. To gain regulatory approval a company has to provide evidence of the drug's safety, and efficacy, combined with a favourable benefit-risk ratio. The patient benefits or patient concerns, especially in the case of cancer, is thus often masked within the clinical endpoints, such as overall survival or progression free survival, or if patient outcomes are measured, they may not be appropriately articulated in dialog between stakeholders, or in publications.

Recent years have seen an upswing in pharmaceutical companies introducing a so-called patient-centric research and focus is shifting towards patient relevant endpoints. However, pharmaceutical companies do not always fully understand how such patient-centric research is to be conducted, and if data is collected, how to interpret the data and how to present the data to stakeholders. The two most important pharmaceutical drug regulators and approval bodies, at least in terms of millions of lives they potentially affect, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) have both in the recent years embraced the concept of patient-centricity, and patient experience in their guidance to the industry. There is an increased acceptance of this type of evidence in regulatory submissions, thus, opening opportunities for pharma companies to promote research towards patient relevant endpoints and evidence.

It is with this background that this thesis is written and compiled, with the aim of discussing how Patient Reported Outcomes (PRO) research can, and should be integrated into pharmaceutical drug development, and how such results can be presented, while keeping in mind the many different stakeholders that need this information, ranging from regulatory agencies, to payers, physicians and patients. The thesis makes use of eight recent patient-centred papers published in the field of prostate cancer.

The papers and the research make a number of important contributions by providing examples of different approaches on how the PRO analyses are conducted, exploring different way of reporting results and by linking the results of PRO evidence to clinical outcomes. Through the iterative learning process, which came as a result of the research I conducted over time and by exploring different analyses methods, ways of presenting results and presenting results to different journals, I learnt how to conduct this type of research, all the way from conceptualization, through data collection, analyses and reporting of results. Thus, by combining this learning, which was gained from this research, with the papers selected for this thesis, this has provided me with the structure and learning and legacy that I can bring forward from this research. It provides the basis for the construct of the framework presented in this thesis for how such Outcomes Research can be implemented in drug development. This blueprint and framework can be adapted to any disease area and can enhance the impact of the research, enhance new drug treatments, and help patient's get the best and most suited treatment options.

As an overall mantra of clinical drug development, we must embrace that the ultimate *raison d'etre* of any medicine or intervention, must be to the benefit of the patients and to improve their health.

Acknowledgements

I would like to thank my academic advisor, Professor Francis Fatoye for his support, encouragement and guidance throughout the process of this thesis. I also like to thank my ex-colleague and valuable peer, Professor Isaac Odeyemi for his continuous support throughout my career. Furthermore, I could not have done this without the support of my dear wife Susan and my inspiring children, Marianne and Fredrik. Lastly, I want to thank my dad Leo, who has been an inspiration throughout my life.

Chapter 1: Introduction

1.1 Prostate cancer challenge

Prostate cancer (PCa) is one of the most common cancers in men both in Europe (Ferlay et al., 2013) and worldwide (IACR, 2012). Moreover, in 2012, PCa represented the third most common cause of death from cancer in men in Europe (9.5% of the total) (Ferlay et al., 2013) and the fifth leading cause of death from cancer in men globally (6.6% of the total) (IACR, 2012). Furthermore, PCa and metastatic PCa represent a significant burden to individuals, families and caregivers as well as healthcare systems in terms of costs (Alemayehu, 2010; Le, 2013; Luengo-Fernandez et al., 2013) and healthcare resource utilisation (Dass, 2012).

Patients with metastatic PCa have a poor prognosis (Bracarda et al., 2011, Heidenreich et al., 2013, Kälin, 2011) and historically, the median survival was <2 years (Cookson et al, 2013). In the majority of patients with PCa, a number of disease- and treatment-related symptoms adversely affect Health-Related Quality of Life (HRQoL) (Payne, 2012, Holmstrom et al., 2018) which deteriorates as the disease progresses (Merseburger et al., 2013; Sullivan et al., 2007). Skeletal metastases represent a substantial burden, occurring in >90% of CRPC patients (Gater et al., 2011), and degenerate QoL, functionality and longevity in patients with mCRPC (Autio et al., 2012).

While new prostate cancer treatments have been made available in recent years, greatly improving the life of PCa patients and prolonging their life expectancy, the extra choice of treatments also makes it harder for the treating physician, the payers and the patient to judge and understand which treatment option provides the best benefit-risk balance and is the most cost-effective. This is where Patient Reported Outcomes (PRO) data, if available and articulated in a comprehensive way can make a difference by providing patient relevant information to help decision making on benefits and risks.

Prostate cancer and the disease progression constitute many different patient segments ranging from early disease, non-metastatic prostate cancer, patients still not treated with any

drug and still hormone sensitive, to the most advanced stage of chemo-therapy resistant, metastatic prostate cancer patients (mCRPC). For clarity of the thesis, these various patients' segments are not specified in the thesis, as the different segments are irrelevant to the scientific question and hypothesis at hand. Hence, the reference to Prostate Cancer, regardless of disease segment or sub-group, will simply be given as PCa throughout this thesis, except for a few instances where it makes sense to specify this.

1.2 Aims of the Thesis

The aim of the thesis is to demonstrate and discuss how the use of PRO data in pharmaceutical drug development can enhance the understanding of prostate cancer during the disease progression.

The PRO data will help differentiate between treatment options and articulate patient relevant impact of treatments, both positive and negative impacts and outcomes, thus reducing uncertainty in decision making for stakeholders. The stakeholders, representing the target audience for the PRO papers will include regulators, such as the FDA and EMA, Health Technology Assessment Bodies (HTABs), payers, physicians, caregivers and of course the patient. The papers used in the thesis as examples of PRO related research communication will provide added clarity of the benefits of the drug to the stakeholders, and thus facilitate their decision making on how to effectively use the drug, and help drugs gain faster approval, faster reimbursement and as a result reach patients faster, which help improve patients' lives. Thus, the audience for all of these papers have been the stakeholders in patient care decision making, ranging from the patient, the physicians, HTABs, regulators and payers.

With my position as an Outcomes Researcher within the pharmaceutical industry, the natural focus, and many times the only means to conduct Outcomes Research is by using PROs in our clinical trials. A more holistic view on the Patient Experience, including the caregiver and other outcomes such as patient preferences, is sometimes possible to include in pharma research, although this requires a bigger logistical effort to get acceptance within companies and thus more challenging to implement. The exception perhaps being qualitative patient

interviews. As mentioned earlier, the industry, including my own company is now waking up to the concept of Patient Centricity, which means the trend is for the wider concepts of Patient Experience, Patient Preferences, Caregiver Experience and other Patient Outcomes, gaining in understanding and thus acceptance and can be more broadly built into the clinical trials in the future. However, in the context of this thesis and what has been technically possible to integrate in my research is first of all and foremost PRO based research. Despite the constraints of focusing on PROs and PRO outcomes, I have been able to implement PROs in all clinical studies and also actively managed an evolution of our clinical research on how the PROs are implemented, analysed and reported on in our prostate cancer studies. This evolution will become evident through the papers I have chosen to build the thesis on.

The thesis will use eight papers, where the present author was the key instigator and sole health outcomes member of the primary research team (clinical team), and a co-author in all papers. The clinical teams are multi-disciplinary teams with representatives from medical, regulatory, toxicology, statistics, and other departments, each represented by, mostly, a single person, or subject matter expert. As I was the subject matter expert, and only Outcomes Researcher in the clinical team, the implication of this was that I was the person who conceptually planned, integrated the plans and ensured the analyses were undertaken and reported from the Outcomes Research conducted in the trials.

This responsibility called for clear conceptual planning of the research. This included the endpoint and PRO instrument selection, securing the implementation of this in the clinical studies, followed by the compilation of the statistical analyses plan (SAP), which most of the time was written as a separate PRO focused SAP, different from the primary SAP which reported on the key clinical finding. This was followed by ensuring the data was collected, then conducting the PRO analyses as per the SAP and finally reporting the results. Once the results are understood, publication were planned together with the larger clinical and medical team. Most often, the primary clinical paper reported on only a small part of the PRO results. Therefore, the aim for me was always to secure additional papers were published, where the focus was on the detailed PRO results. These publications, by nature of this

process will only be focused upon, after the primary paper, which reported on the primary endpoints.

Through this research, which spanned some six to seven years, it was possible to evolve and learn from one study to another. This was particularly true when it came to how the analyses plans, the SAP of the PRO data were constructed and executed. The papers thus provide both the substance and examples for how PRO can be analysed and reported on, as well as address some further aims and objectives of the thesis, such as:

- How can pharmaceutical development integrate PRO research more effectively?
- How are conceptual models for patient signs, symptoms and impacts built?
- How do we prospectively define HRQoL analyses in pharmaceutical research?
- How can HRQoL data most effectively be presented, using different analyses models?
- Can we link clinical relevance of high impact safety complications and the association between HRQoL and clinical outcomes?

As a conclusion of my work and the thesis:
The use of PROs in pharmaceutical drug development enhances the understanding of disease progression and provides means to improve the outcome of patient's care, by articulating patient relevant impacts, and through this data reduce uncertainty in decision making and thus facilitate and expedite access of new treatments to patients.

With this background, the purpose of this thesis is to advance the understanding of PRO data, enhance the common knowledge of how to analyse the evidence and how such research can be integrated into pharmaceutical development in prostate cancer. The thesis will provide examples and guidance as to how PRO research can be implemented in drug development, showcase the value of conducting different types of analyses of the PRO and HRQoL data and how this can all be tied into more patient focused information, as well as clinical outcome relevant end points. It is a complex area and simple messages and solutions are not easily available, hence the needs of the different stakeholders will require different type of analyses and different type of evidence made available to them. All of my eight papers I selected to

support my thesis will together build a framework for how PRO research can be conducted to cater for these stakeholders.

1.3 Patient in the focus of pharmaceutical research – Patient centricity

The role of the patient and patient reported data, and the concept of patient centricity is one of the key focus areas and buzzwords in today's pharmaceutical industry and in drug development. The pharmaceutical industry, in collaboration with the regulatory agencies such as the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) are taking steps to provide guidance and improve ways medicines are developed as well as the methodologies used to analyse the data collected from the patients through the patient reported outcomes information. With these measures, the patient, as a key player in the treatment paradigm, is brought forward, and information directly relevant to the patient is developed and presented in a way better understood by the patient, as well as decision makers.

Due to an ever-increasing cost of health care and drug cost, in oncology in particular, while at the same time there are limited healthcare resources and increasing doubts of the benefit and cost-effectiveness of many new drugs, estimating the economic and humanistic burden of treatment is extremely important. In particular, by providing information and evidence of the drug benefit, and the patient benefit of the treatments, and by providing it in understandable formats will decrease uncertainty and help decision making by stakeholders. This is critical for all stakeholders, such as healthcare policy makers, health systems, physicians, patients, employers, and society overall. It is in this context that the patient reported outcome information plays an important role. As part of the multi-factorial decision-making the role of PRO derived information can help articulate differences in treatment options and thus, the request for such information and use of it has increased significantly in the last years (Basch, 2018; Gnanasakthy and DeMuro, 2015; Shields, 2016)

Any data derived directly from the patients is defined as Clinical Outcomes Assessments (COAs) or Patient Reported Outcomes (PROs). The concept of a COA is the broader of the two and is defined by the FDA (Food and Drug Administration) (FDA, 2009) as:

Clinical outcome assessment — A COA is any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit. Unlike biomarkers that rely completely on an automated process or algorithm, COAs depend on the implementation, interpretation, and reporting from a patient, a clinician, or an observer. The four types of COAs are patient-reported outcome (PRO) measures, clinician-reported outcome (ClinRO) measures, observer-reported outcome (ObsRO) measures, and performance outcome (PerfO) measures. (Walton et al., 2015)
The Patient Reported Outcomes - Patient-reported outcomes (PRO) is an umbrella term that includes outcomes data reported directly by the patient. It is one source of data that may be used to describe a patient's condition and response to treatment. It includes such outcomes as global impressions, functional status, well-being, symptoms, health related quality of life (HRQL), satisfaction with treatment, and treatment adherence (Walton et al., 2015).

The two concepts of PRO and COA, and their relationship to each other are illustrated in the Figure below (Figure 1). In the context of this thesis, the more relevant of the two is the PRO, as it is a direct measure of the Health-Related Quality of Life (HRQoL), or the Quality of Life (QoL) as reported by the patient. By definition, and strictly speaking, the QoL and HRQoL are not exactly the same thing but are frequently used interchangeably. In health care, the HRQoL is an assessment of how the individual's well-being may be affected over time by a disease, disability or disorder. Throughout the thesis, the use of "PRO instrument", instruments", "PRO questionnaire" and "PROs" are to be read as synonyms. The meaning and intent of these are the same.

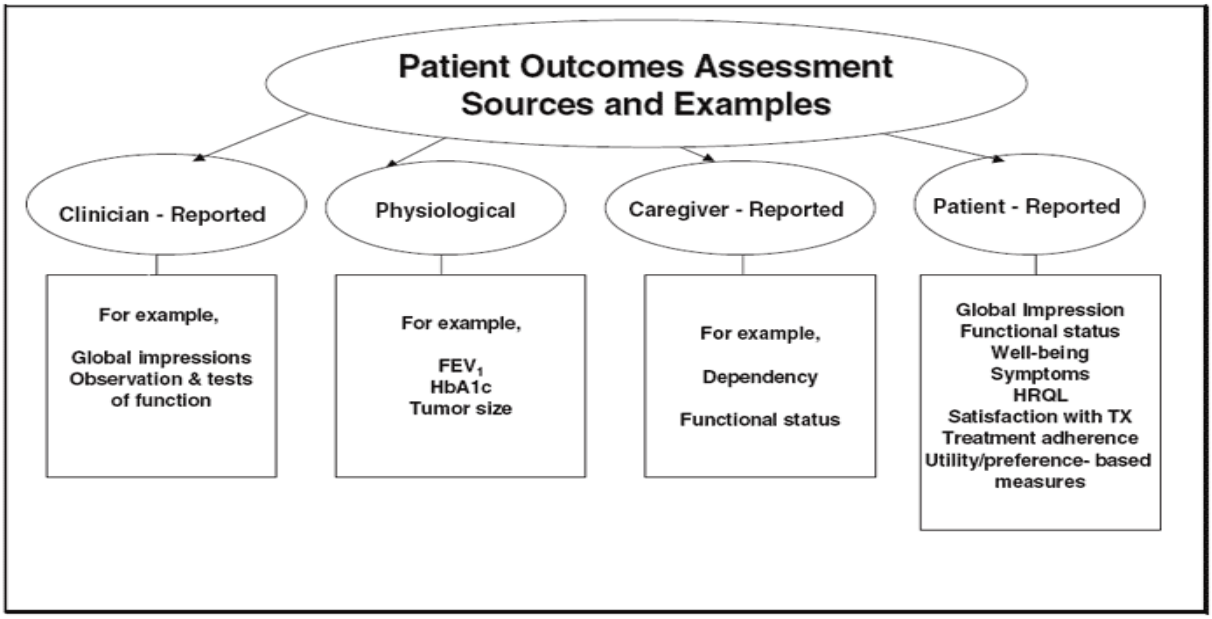

Figure 1.1 Patient outcome assessments types (COA) (from Acquadro et al, 2003, page 524)

1.4 Patient reported outcome instruments in prostate cancer

Of all disease areas, perhaps cancer has one the one most profound effect on the patient and thus is extremely relevant when it comes to how a disease and treatment affects the patient's Quality of Life. To have the diagnosis of cancer will already significantly affect the patient, given the common knowledge and understanding of the gravity of the diagnosis (Flynn, 2013). Any subsequent, additional burden to the patient should be avoided.

In addition, at the end-of-life stage one must also ensure any negative treatment effect is out-weighted by a significantly improved life expectancy and/or improvement, or stabilisation of the quality of life. Life expectancy of cancer patients has fortunately been increasing over the years with the introduction of new treatment modalities. The increase in life expectancy will vary from disease to disease, but in advanced prostate cancer today, a minimum of 3 months increase in overall survival is expected, should a new treatment be regarded as providing additional benefit to existing drugs. New drugs also need to out-weigh any negative treatment effects or side effects. Some cancers, such as gastric cancer may be in a more fortunate situation and patients can expect several months (6-12 months) increase in survival. Others, such as breast cancer or blood cancers have now access to treatments that can increase life

expectancy with several years, or even cure the disease (Flynn, 2013). The implications are thus for prostate cancer, given an increase in cost of these treatments, that patients should truly benefit from the new treatments while society can expect to be using limited healthcare resources wisely. This further strengthen the need for patient relevant information to enable educated decision-making.

To measure and assess QoL in PCa is best done by combining two types of PRO instruments. First with a Non-disease specific instruments, and secondly with a Disease specific instruments. The non-disease specific or generic instruments can be used for any disease and will use general questions to measure QoL. The disease specific ones will include signs and symptoms bother that is specific to one disease. These two types of instruments will provide both a comparative assessment of how the disease impacts the patient, as compared to other diseases, while the disease specific questions will drill down on specific symptoms that are relevant, in this case in prostate cancer.

Examples of the Non-specific instruments are:

- European Quality of Life 5-Domain (EQ-5D) questionnaire
- Functional Assessment of Cancer Therapy–General (FACT-G) questionnaire
- European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQC30),

Examples of Disease specific instruments are:

- Functional Assessment of Cancer Therapy–Prostate (FACT-P)
- European Organization for Research and Treatment of Cancer (EORTC) QLQ-PR25, prostate cancer questionnaire.

The studies done with enzalutamide in prostate cancer have made use of these instruments as well as measured pain, through a pain instrument called Brief Pain Instrument (BI).

1.5 Integrating PROs and payer relevant endpoints in pharmaceutical development

The clinical research in pharmaceutical drug development is done in defined phases called phase 0, phase 1, phase 2, phase 3 and phase 4. The phase 0, phase 1, phase 2 and phase 3 are

designed to collect evidence on the drug safety, efficacy and tolerability and will complete the regulatory submission made available to regulatory authorities across the globe. The phase 0 – 2 is where dose, dose regiments, primary efficacy measures, effect size and endpoints are explored and confirmed. If no safety concerns are found in the phase 1 or phase 2 studies, the research moves into phase 3, usually consisting of at least two large, multi-center, randomized and double-blind studies (RCT's). These RCT's are designed to provide all necessary clinical efficacy evidence for obtaining the regulatory approval. Important point to note is that the RCT's focus on clinical efficacy, not cost-effectiveness. The RCT's will include thousands of patients, except for rare or orphan disease indications where the total number of patients may be smaller. Endpoints and measures used in the phase 3 studies should all be confirmed and validated and thus provide solid scientific evidence of the safety and efficacy and include sufficient data on the patient relevant outcome, including PRO derived information. Once the regulatory submission is done and regulatory approval has been obtained, the companies continues to conduct clinical studies, and these are referred to as phase 4 studies.

The pharmaceutical companies have for many years, and to some extent still today focused the phase 1 to phase 3 research mainly on obtaining the regulatory approval, in other words not fully considered the needs of Health Technology Assessment Bodies (HTABs), other payers and patients. The regulatory data package, especially when conducted as placebo-controlled studies, has always been less relevant and less informative for the HTABs, payers and patients. The placebo-controlled studies pose a specific problem because comparative data with other treatments options is missing. Payers and patients need to understand what different treatment options provide and how they differ from each other. In placebo-controlled studies this reference point and comparative aspect is not covered and hence provides only out-of-context information. The regulatory submission to the US Food and Drug Administration (FDA) and the European Union (EU) European Medicines Agency (EMA), will clear the first hurdle, but has not always been met with approval, or facilitated the reimbursement submissions. About 20% of Health Technology Assessments (HTA) made by UK National Institute for Health and Care Excellence (NICE) are not recommending the drugs for use, although EMA has already granted regulatory approval for these drugs (NICE, 2018).

Research reported in 2013 found that despite the call for inclusion of more patient centric research the studies including PROs remained relatively low (between 30-35% of studies) and the trend in the years dating back to early 2000 and up to 2011 remained the same (Brim and Pearson, 2013). While analysing the [European Organization for Research and Treatment of Cancer] (EORTC) and their RCT's it has been shown that the inclusion of PRO and HRQoL instruments has however increased over the period of 2002-2013, and this has contributed to altering clinical practice and support and help obtain regulatory approvals for oncology trials (Zikos, 2014) . In a more recent paper from 2017, it was noted that in drug approvals between 2009-2013, still, unfortunately a majority of drugs entered the market without evidence of benefit on survival or QoL (Davis et al., 2017).

The importance of the PRO data as a relevant and informative part of the decision-making has many recent examples. In December 2017, the Chairman of the German Federal Joint Committee (G-BA) noted that the G-BA like to see QoL more strongly considered in the assessment process. The G-BA noted that one-fifth of the eighty-eight oncology medicines that have undergone a benefit assessment procedure are judged not to show an added benefit and suggest oncology drugs should in fact be negatively assessed if their submission do not include information on Quality of Life. (GB-A, 2017)

Recent thinking includes building up an endpoint strategy, including a PRO and patient centric strategy. The most important question to ask when building up an endpoint strategy and for focusing the data points in studies will be; what does one want to say about our drug? An endpoint model such as the one below can help facilitate dialog with stakeholders, and to link, and integrate PRO building blocks into the research program of new drug development (Sheilds, 2013).

Table 1.1: Adapted End-Point model for clinical development program, a hypothetical model. The model outline how primary and secondary claims will be defined as endpoints, and how they can be measured.

Claim	**Concept**	**End point**	**Assessment type**

Primary endpoints			
Treatment reduces tumour size	Tumour size or death	Progression free survival is defined as time from randomization to first documented disease progression	MRI/CT scan Date of death
Secondary endpoints			
Treatment improves disease related symptoms by X points compared with other treatment	Pain	Proportion of patients with >50% reduction in pain score from baseline to week 18	PRO instrument

Source: Shields et al., 2016 (page 191)

Endpoint models, such as the one described above can greatly help in designing and conducting research that is better designed and adapted to other stakeholder needs, including the HTABs, payers and the patients.

In this thesis, I build a framework for how to conduct HRQoL and PRO research in prostate cancer, by building on my papers in this field. The basis is to include PROs in clinical research, reach out to the patients for qualitative patient interviews, analyse the PRO data in multiple ways and finally bridge the patient reported outcomes and benefits to clinical endpoints. Eventually this can enhance how prostate cancer research is conducted and greatly benefit the patients as well as save health care resources.

1.6 Overview of publications and contribution of these to the thesis

At the time when this Outcomes Research on enzalutamide in prostate cancer started, there had been no new treatment modalities, no new medical treatments introduced for prostate cancer for many years. Thus, limited opportunities had existed in terms of advancing the field of Outcomes Research in prostate cancer. The field was therefore mature for input and

knowledge sharing, partly by providing educational material on how to conduct Outcomes Research in this space, such as I have reported in papers 1 and 2, and partly through reporting on the effect of the new treatment of enzalutamide in the various stages of prostate cancer, as I have done with papers 3, 4, 5 and 6. Furthermore, these earlier papers provided the opportunity to further explore the link of HRQoL outcomes and clinical endpoints, as well as providing patient relevant information on the effect of the drug through item analyses, as done in papers 7 and 8.

All of the papers included in the thesis have, therefore, been included with a clear rationale. Together they build up a story of how enzalutamide works in prostate cancer, as well as providing a framework for how PRO integration in drug development can be conducted in order to provide more meaningful and understandable information to the patient, physician and other stakeholders, and thus increase the impact of the results. As mentioned earlier, the focus in the research, and in this thesis is on PRO results as the only available proxy for the wider concept of patient experience. Ideally, other patient experience measures, caregiver experiences or wider patient-centric outcomes, including for instance societal aspects or patient preferences, should be included in such research. However, the pre-requisite for a successful implantation of such a broad Outcomes Research focus is to work with a well-established clinical team with previous experience with such work, and thus work with a team with an advanced understanding of the benefits of Outcomes Research and not having to extensively educate the team of the meaning of each work. It also requires access to sufficient funds and resources, both when it comes to economic and humanistic support.

Another, quite unique aspect that enabled this research to be conducted in the whole complexity as reported in these papers, was the ability to follow one compound and one line of research for a longer time-period. Outcomes Researchers in the drug industry are very seldom able to follow a full life-cycle for one compound, meaning that one may be included in a few studies, perhaps in the development of one indication, but rarely in many studies and covering a whole range of indications. The fact that I was able to follow enzalutamide from the very early clinical studies and first disease stage, to the later disease stage studies, several years down the line, provided me with a unique opportunity to conduct this research, building on results and experience, one after the other, and learn from previous mistakes.

The framework, which is part of the conclusion of my thesis, is thus building on the experience gained from this opportunity and all the Outcomes Research I conducted throughout the years.

When the research and the first papers were initiated and conducted, the clinical team had very limited understanding of how Outcomes Research should be conducted, or even why this type of research needed to be done, given that regulatory submissions did not require such data. In general, pharma companies still today struggle to meet these needs, especially in small start-up companies where a global mind-set and understanding of HTABs, or other stakeholders' needs is not well established and thus these endpoints are often omitted. In Chapter 3, **Paper 1** addresses these shortcomings and guides industry researchers on how to plan, integrate and conduct HTAB relevant evidence generation research.

As an Outcomes Researcher I deemed it necessary to have a high-level and focused guidance in order to guide the internal discussion on Outcomes Research and in general on Health Economics and Outcomes Research (HEOR) in the public domain. This paper therefore created a foundation for what the HEOR team should focus on, and why. Without this basic understanding, the clinical teams would have continued to struggle to understand the need for this research.

Paper 2 in Chapter 3 reports on the construct of the so-called conceptual model based on qualitative research from patient interviews. This is the first step one should take in any disease area, not well documented in publications. The clinical team that I was working with at the time had no direct experience or previous exposure of this type of research. In addition, only limited resource and budget was provided for my Outcomes Research plans. As a consequence, I struggled to conduct state-of-the-art research, such as outlined in the ISPOR guidance (Patrick et al., 2011a; 2011b). The paper reflects these shortcomings. At a later stage, one of our subsequent research papers, albeit a different disease segment, (Holmstrom et al., 2018) would become a better reference for such research. The later paper is evidence for how my evolution in the conduct of Outcomes Research and qualitative research has progressed.

Qualitative patient interview research will consist of two steps. The first one is the conduct of a full systematic literature review, or alternatively a targeted literature review, to ensure one has a full comprehension of what has already been published and discussed in the terms of patient reported symptoms and impacts of the disease. The second phase is to conduct interviews with, both clinicians specialised in the treatment of the disease and secondly, and with patients with the disease. This is included in Chapter 3 discussing the integration of PROs in PCa research.

Moving on to Chapter 4, **Paper 3** reports on the analyses and results of the QoL results from the prostate cancer clinical phase 3 study of PREVAIL (PCa). The paper reports on our results from the second large phase 3 study, with focus on the PRO and HRQoL data. This paper represents the first effort to separate the PRO and HRQoL results from the so-called primary paper whilst publishing a scientifically interesting paper focusing on patient outcomes, rather than clinical endpoints. The paper covers all of the HRQoL results, while also graphically representing the results as a time-to-event and change from baseline graph. The analyses performed was focusing on the instrument specific scoring algorithms. This classic approach for reporting the PRO results, focus on the composite scores resulting from the pre-defined scoring guidance. This will always be instrument specific. The FACT-P instrument will report so-called “Total Score”, which is a composite score summarised from 39 different items. While these are very informative in providing trend analyses and a graphical illustration of the impact of the disease progression under different treatment arms, it is not always easy to understand what these results mean for the patient.

Paper 4 in Chapter 4 reports on the QoL results in the prostate cancer phase 3 AFFIRM PCa study using a different methodology. At this stage of my research I had access to two of our larger phase 3 studies (AFFIRM and PREVAIL), and the data quantity started to build up. I discussed extensively with the clinical team how we could best analyse the PRO and HRQoL data, and equally, how I could best represent the data in a meaningful way to cover the interests of different stakeholders and different readers. The results from the studies indicated a clear benefit of enzalutamide over placebo, while no harmful effect was identified. However, scientifically we must understand what drives the positive results from enzalutamide, while also ensuring the signal was real. In this study I included testing on

missing values, sensitivity analyses and different way to graphically present the results. The Mixed Effects model for Repeated Measure (MMRM) as well as a Pattern Mixture Model (PMM) were applied as a secondary analysis to address missing values issues. The paper also explores the way results are presented using not only longitudinal change from baseline graphs, but also using a Cumulative Distribution Function (CDF) to enable an easy overview of the two populations (treated versus placebo) and the population response.

The last part of Chapter 4, **Papers 5 & 6** provide new information not reported before. Firstly, by providing comparative information relevant to other treatment options and secondly by highlighting the clinical aspects of key disease related symptoms, that of Skeletal Related Events (SREs). The SREs are mostly due to metastasis in the bone, or bone fractures. These studies were only achieved through my extensive and persistent dialog with the clinical team on how we can best dialog with stakeholders on relative effectiveness terms. For HTABs and payers, there are two important aspects when making decisions on the use of enzalutamide, or any new drug, should the drug be used, and is the benefit, risk and cost justified? Firstly, questions related to how enzalutamide compares to other active treatments of PCa (**Paper 5**). Secondly related to cost and possible economic cost-savings or other benefits the drug may provide (**Paper 6**). For both of these aspects the papers use the Outcomes Research endpoints, to highlight the benefit of enzalutamide. The comparative data is also very important and relevant for the treating physician and for the patient, enabling the patient to be part of a decision on how to pursue treatment of the prostate cancer. Both papers providing comparative data on both benefits as well as safety concerns. These two papers complement the Chapter 4 on Analyses of the PRO instruments.

The common themes and foci in all previous papers was to explore various ways of analysing the PRO data, analysing the impact of missing data, as well as graphically presenting the data in different ways. Based on the analyses, I was able to say that overall QoL scores were positive and showed a benefit of enzalutamide over placebo. However, questions that remained unanswered was, what was driving this positive effect for the patient and can we identify single item improvements, which are relevant to the patients, as the drivers of this effect?

As a next step, I therefore took a deeper dive into the different domain and item analyses of the PRO results. The opportunity that had opened up for this type of research, was in part driven by new guidance received from the FDA (FDA, 2017). However, in addition to this, the other key question was to show how HRQoL and PRO results could help the clinician understand and relate to the PRO data by linking PRO results with clinical outcomes. Therefore, the last two papers (**Papers 7 & 8**) in Chapter 5 report on different ways of analysing the PRO data as well as investigating the association between HRQoL and overall survival (OS) and radiographic progression free survival (rPFS). **Paper 7** is an example of what I believe is the current trend in the field of PRO and HRQoL research today. The current trend is to make use of all items in a PRO instrument, not just composite summary scores, while analysing them as individual items and looking at impacts that are relevant for the patient while, expressing the results in such a way that is more intuitive for the patient and physician to understand. **Paper 8** also brings in the physician relevant information into the overall picture of PRO research by making associations between endpoints used by the physician, such as the OS outcome associated with PRO outcomes. If PROs can be used as a prognostic factor of outcomes this will be of great value to clinicians. Work has been done on using QoL as prognostic of baseline value, but few on over-time values of QoL measures.

While discussing with clinicians the meaning of PRO and HRQoL data, in my experience, there is often a lack of understanding of what the data mean for them as clinicians and how to interpret the data. While they all agree that measuring QoL as part of the treatment benefits is important, the PRO data fails, as currently reported, to make it relevant for the treating physician. Thus, by creating the link between clinical outcomes and the outcomes from PROs, this will greatly enhance the acceptance of PRO data among clinicians and in particular if the HRQoL data can be used as prognostic factors.

1.7 Chapter summary

This chapter has given an overview of the landscape of PROs, what PROs are, how they are used in prostate cancer. In addition, it discusses how PROs are used for serving the needs of both regulators and payers and how they help define an endpoint model for drug development, which in turn guides the overall clinical study design. It introduced the challenges the industry

has been facing with the integration of PROs in drug development and how the regulatory environment is currently changing and embracing more patient centricity in their assessments of new drugs.

With my publications in PCa, and through the gradual increased understanding of both the compound, enzalutamide, as well as how to best analyse the PRO data, the papers re-create the story-line as to, what PROs to include, how to analyse the data and how to represent the data through graphical and other means for stakeholders to understand. At the same time, there was an increased awareness within my company for how to conduct Outcomes Research; which facilitated possibilities to conduct the PCa related research and get acceptance for publishing the work, in its own right.

It is also important to understand the regulated environment the pharma industry has to live within while conducting clinical research. To improve the patient centred research and improve PCa outcomes using PRO data need to consider these constraints.

The next chapter will be discussion the Epidemiology and Burden of the Disease of Prostate Cancer. As one of the four most common cancers in the world, it takes an important position in the overall burden on health care resources and in terms of patients impacted.

Chapter 2: Epidemiology and Burden of Disease

The chapter 1 laid the foundation of understanding the importance of prostate cancer and the need for advancing the treatment of prostate cancer in order to reduce number deaths and improve patients' lives and their QoL. The chapter has also given an overview of the world of PROs and how these fits with pharmaceutical drug development, helping companies to become more patient centric. This chapter will provide an overview of prostate cancer, the disease burden and epidemiology of the disease.

2.1 Overview

It is estimated that 8.2 million people died from cancer worldwide in 2012. The most common cancers are lung, bowel, breast and prostate cancers. Together they accounted for almost half (48%) of all cancer deaths in the UK in 2014 (Flynn, 2013). The physical and psychosocial effects of Prostate cancer are profound for patients and their families and spouses (Flynn, 2013). This includes skeletal related events (spinal cord compression, bone metastases), lower urinary tract symptoms, fatigue, pain and a few other related events. In the majority of patients with Prostate cancer, a number of disease- and treatment-related symptoms adversely affect HRQoL, which is diminished compared with the general population, and QoL deteriorates as the disease progresses (Merseburger, 2013).

In a population-based cost analysis, the economic costs of all cancers to the European Union (EU) was €126 billion in 2009; the cost associated with Prostate cancer was the fourth highest at €8.43 billion (7% of overall cancer costs) (Luengo-Fernandez et al., 2013). Cost estimates included care in the primary, outpatient, emergency, and inpatient settings, drugs, unpaid care from relatives/friends, and lost earnings.

The treatment landscape of prostate cancer changed dramatically a few years ago when new androgen signalling agents such as enzalutamide and abiraterone entered the market. Except for bicalutamide and androgen deprivation treatments, the options for advanced prostate cancer has long been chemotherapy. Chemotherapy has a high burden on the patient in

general and avoiding chemotherapy or delaying such treatment will in general be a desirable outcome. The distribution of patient age and incidence of prostate cancer as shown in Figure 2.1 corresponds well with the population included in the clinical studies AFFIRM and PREVAIL.

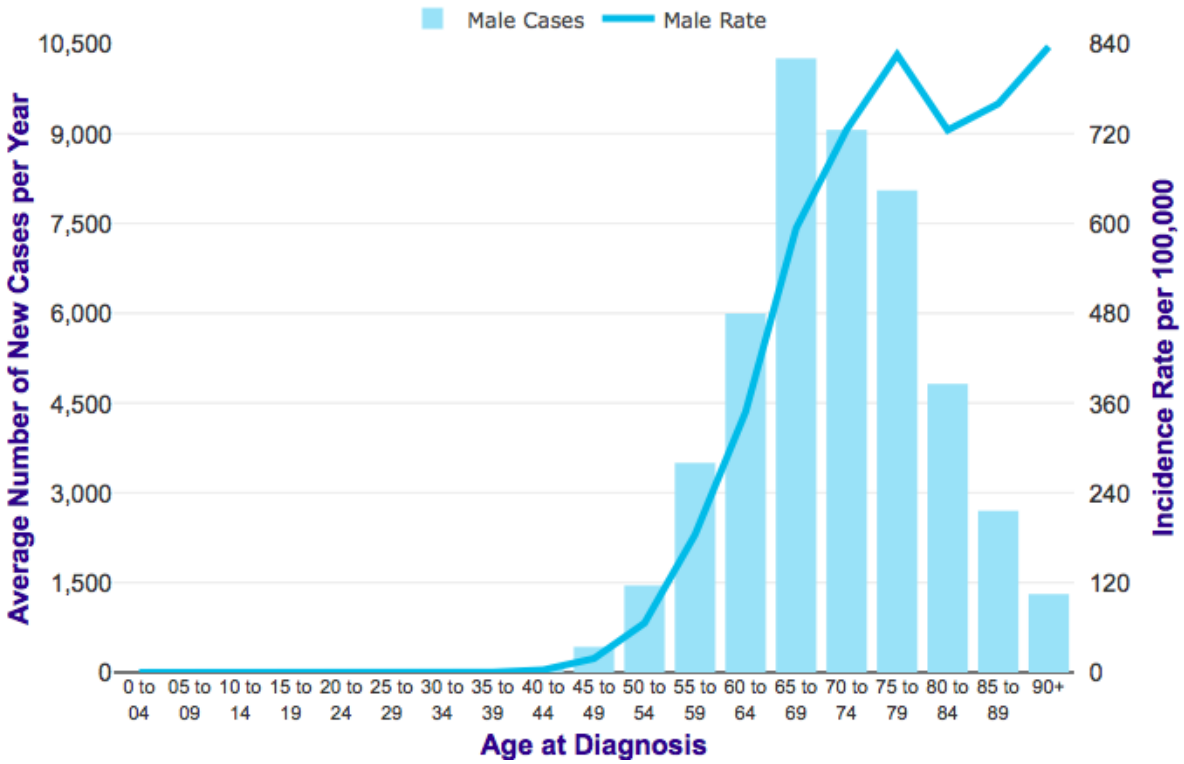

Figure 2.1: PCa 2011-2013 average number of new cases per year and age-specific incidence rates per 100,000 population, males, UK (UKCR, 2014).

2.2 Prostate cancer and hormone resistant prostate cancer

Androgen deprivation therapy (ADT) is first-line treatment for advanced/metastatic Prostate cancer. In recent years, luteinising hormone releasing- hormone (LHRH) agonists have been the most commonly used form of ADT in advanced Prostate cancer. More than 80% of patients show a positive response to androgen ablation (Heinlein and Chang, 2004). However, despite this good initial response, disease progresses despite continuous hormonal manipulation after around 2–3 years (Amaral et al., 2012; Karantanos et al, 2013). The median age of men with prostate cancer is in the 70s (Toren and Gleave, 2013) and skeletal

metastases occur in >90% of prostate cancer patients (Gater et al., 2011). In contrast, based on US data from the Surveillance, Epidemiology, and End Results (SEER) database, only ~4% of all newly diagnosed patients present with metastatic Prostate cancer (NCI, 2014; Toren and Gleave, 2013; NCRAS, 2012).

In the past, various terms have been used to describe Prostate cancer that relapses after initial ADT; these include androgen-independent Prostate cancer, hormone-refractory Prostate cancer, and hormone-independent Prostate cancer. In recent years, these terms have been superseded by the term 'castrate-resistant Prostate cancer' (CRPC).

Metastatic castrate-resistant prostate cancer is the terminal stage of PCa, and patients at this stage with prostate cancer have a poor prognosis (Bracarda et al., 2011; Heidenreich et al., 2013; Kälin, 2011). Metastatic PCa median survival for men has been less than 2 years (Cookson et al., 2013). As the disease progresses, quality of life (QoL) deteriorates.

As stated earlier, and for the purpose of this thesis, there is no distinction between the different stages of prostate cancer when analysing the PRO results. All are reported throughout the thesis under the umbrella of PCa.

2.3 Epidemiology

Epidemiologic trends in Prostate cancer may reflect changes in age and Prostate cancer stage at diagnosis over recent decades. Specifically, men are being diagnosed at younger ages, and in the USA for example, the rate of stage IV disease has increased among the younger population (Cetin et al., 2010). Worldwide, Prostate cancer is the second most common cancer in men and the fifth leading cause of death from cancer in men. Within Europe, Prostate cancer incidence rates are highest in Northern and Western European countries and the lowest in Central and Eastern European countries (IACR, 2012). In the USA, incidence and mortality is higher in African American men compared with other racial/ethnic groups (NCI, 2014). It is not clear why this is, but it is believed that diet, genes and hormones all play a part in this (McIntosh, 1997)

Worldwide data indicate that Prostate cancer is the fourth most common cancer in both sexes combined and the second most common in men (IACR, 2012). Thus, in 2012, an estimated 1.1 million men were diagnosed with Prostate cancer globally, representing 15% of all cancers diagnosed in men; almost 70% of cases occurred in more developed regions.

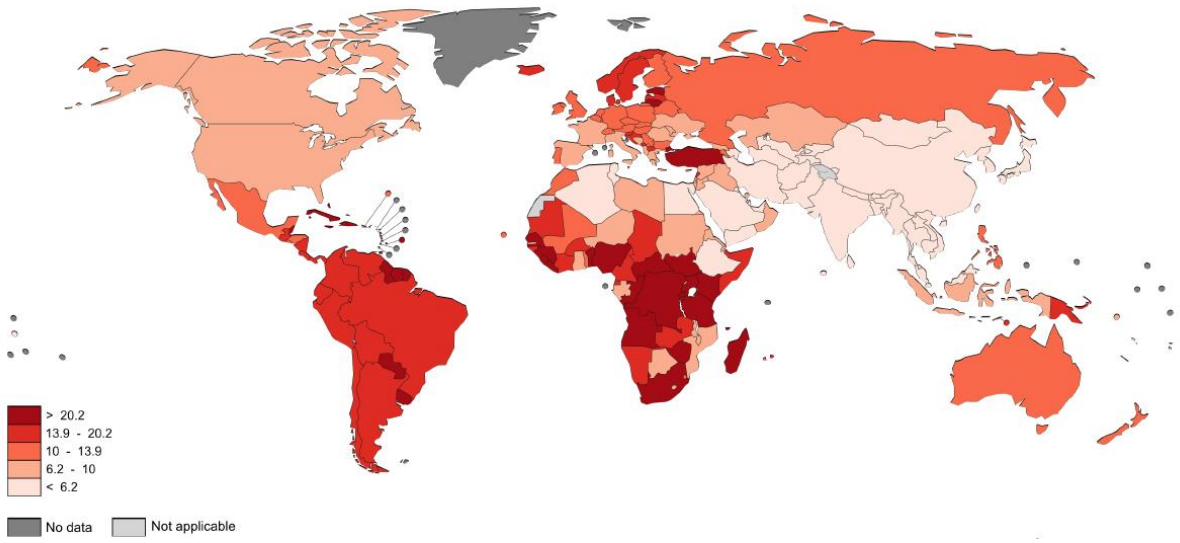

Figure 2.2: Worldwide incidence of prostate cancer mortality 2012.

Estimated age-standardised rates (World) per 100,000 (IACR, 2012)

2.4 Patient burden

Health outcomes were assessed using the EQ-5D in 3,477 Prostate cancer patients (of whom 1405 [40%] had prostate cancer and 1,119 had prostate cancer) in a large analysis across EU-5 countries (2009–2010) (Sternberg et al., 2013). Using EQ-5D VAS scores, HRQoL were poorer in metastatic and prostate cancer patients: averages (out of a possible 100) were 74.8, 71.6, 66.3 and 66.5 for patients with localised, locally advanced, metastatic and prostate cancer, respectively.

The physical and psychosocial effects of prostate cancer are profound for patients and their partners and family (Flynn, 2013). QoL in advanced Prostate cancer has been well documented but studies involving patients with prostate cancer, where appropriate QoL data is collected, has been sparse. In the majority of patients with prostate cancer, a number of disease- and treatment related- symptoms adversely affect health-related quality of life

(HRQoL) (Payne, 2012), which is diminished compared with the general population, and QoL deteriorates as the disease progresses (Merseburger et al., 2013; Sullivan et al., 2007).

QoL outcomes in PCa in Germany were assessed in a 1-year observational, cross-sectional, prospective study in 37 specialised Prostate cancer centres. Interim results from 101 patients showed that the mean EQ-5D visual analogue scale (VAS) score (out of a possible 100) was 47.8. Mean overall EQ-5D single index utility score (which ranges from 0 to 1, where 1 = full health) was 0.72: 0.81, 0.66 and 0.64 for pre-chemotherapy, post-chemotherapy and ongoing chemotherapy patients, respectively. In addition, 67.3% of patients had pain or discomfort, 58.1% problems to perform usual activities, 53.1% mobility problems, 37.7% anxiety/depression troubles and 32.7% self-care problems (Wolff, 2012). QoL was also assessed using the FACT-P tool. The total score (out of a possible 156) was 101.5 and mean subscale scores were; physical well-being, 19.5; social/family well-being, 20.6; emotional well-being, 17.0; functional well-being, 15.7; Prostate cancer subscale, 28.6 (Wolff, 2012).

In a recent UK study in 163 men with prostate cancer, HRQoL data were collected via an online survey and included EQ-5D and EORTC QLQ-C30, supplemented by a 25-item EORTC-8D Prostate cancer–specific questionnaire module (Lloyd et al., 2015). This study stratified patients by disease state. Utility values elicited by the EQ-5D ranged from 0.830 for the asymptomatic/mildly symptomatic pre-chemotherapy disease state to 0.625 for the symptomatic pre-chemotherapy disease state (maximum possible score = 1, full health). EQ-5D VAS values ranged from 77.5 to 56.2, respectively (out of a possible 100). For all of these instruments, utility values/VAS scores for patients receiving chemotherapy or post chemotherapy- were within the ranges reported for the pre-chemotherapy groups.

EQ-5D health status in PCa appears to be lower than the general population norm (Sullivan et al., 2007; Wu, 2007). This was confirmed in two US observational studies using the EQ-5D single index utility score which showed the mean baseline EQ-5D score for patients with prostate cancer to be 0.603 in one study (Sullivan et al., 2007), and 0.64 in a second (Wu, 2007). Both well below the US population norm of 0.87 (Luo et al., 2005), while a score of 1.00 signified best imaginable health. The second study also showed that prostate cancer patients scored lower than population norms on the generic measure, FACT-G, with a total

score of 75.4 (higher score signifies better HRQoL) (Wu, 2007). The US population norm is at 80.1 (Brucker et al., 2005). This confirms the impact PCa has on the patient's well-being, with a progressively deterioration of the QoL of the patients as the disease progress.
Prostate cancer patients also show impairment in most HRQoL domains using cancer-specific instruments. In a multinational, observational cohort study of oncology practices, 280 prostate cancer patients from Australia, Canada, France, Germany, Italy, and the UK were assessed using the EORTC QLQ-C30 and FACT-P Prostate cancer Subscale (PCS) in addition to EQ-5D (Sullivan et al., 2007). As prostate cancer progresses, a decline in HRQoL was observed. Thus, a significant decline from baseline in FACT-P PCS, EQ-5D and 10 of the 14 EORTC domains was seen at 3, 6 and 9 months (Sullivan et al., 2007).

Improved HRQoL has been linked to better clinical outcomes in prostate cancer. Analysis of data from a phase III trial of the endothelin receptor antagonist atrasentan in prostate cancer patients found that better baseline and 12-week change in HRQoL are strongly associated with better survival, time to disease progression and pain prognosis than those with worse HRQoL (Sullivan et al., 2007).

2.5 Impact of skeletal-related events (SREs) on QoL

Skeletal metastases occur in >90% of prostate cancer patients (Gater et al., 2011). Skeletal metastases often lead to reduced QoL, functionality and longevity in patients with prostate cancer (Autio et al., 2012). It has been shown that a higher number of bone lesions is associated with shorter progression-free survival (PFS) and overall survival (OS) in patients with prostate cancer (Tait et al., 2014), and a higher volume of bone metastasis is associated with reduced OS in prostate cancer (Perez-Lopez et al., 2016). Common complications of skeletal metastases include bone pain, vertebral collapse or deformity, pathological fractures, spinal cord compression (SCC) and osteoporosis (which may cause fractures). Because of their high frequency in prostate cancer, skeletal metastases are responsible for a considerable proportion of patient morbidity, primarily through complications known as SREs (Brown and Sim, 2010). SREs (defined as a pathological fracture, SCC, palliative radiation to bone, or surgery to bone (Weinfurt et al., 2005) lead to significant functional declines in patients' daily lives. Patients with SREs experience clinically meaningful declines in physical and emotional

well-being after radiation to bone and pathologic fractures and declines in functional well-being after radiation. SREs were found to impact patients' QoL in metastatic Prostate cancer patients (DePuy et al., 2007); patients with SREs in the initial period had significantly worse HRQoL than those without SREs.

2.6 Cost of illness and Economic Burden

As the new treatments of prostate cancer and for cancer in general are approved, the associated cost of treatment is increasing. Therefore, estimating the economic burden of cancer is increasingly important for healthcare policy makers, health systems, physicians, employers, and society overall to enable decisions on treatment options to be evidence based. In a population-based cost analysis, the economic cost of all cancers to the EU was €126 billion in 2009; the cost associated with Prostate cancer was the fourth highest at €8.43 billion (7% of overall cancer costs) (Luengo-Fernandez et al., 2013). Cost estimates included care in the primary, outpatient, emergency, and inpatient settings, drugs, unpaid care from relatives/friends, and lost earnings. European cost of illness data in prostate cancer are scarce and costs for prostate cancer patients can be difficult to discern due to the lack of a specific International Classification of Diseases code. However, the recent development and approval of new therapies that improve survival in prostate cancer will likely make the cost of disease management an even greater issue. Implications of this is that more data, such as PRO and QoL data is needed, in order to properly assess the new treatments.

Prostate cancer management and prostate cancer in particular, can be complex, challenging, and costly (Lew, 2013). The cost of prostate cancer varies according to the speciality (urologist or oncologist) and type of physician providing the PCa care (Engel-Nitz et al., 2011). In a retrospective US claims analysis, first-year total adjusted healthcare costs ranged from around $32,000 by a urologist to $54,000 for patients (annual costs in USD) (Engel-Nitz et al., 2011).

2.6.1 Cost associated with SRE's

Patients with bone metastases (>1.5 million worldwide) frequently develop SREs which add a substantial cost to management for healthcare payers. A Belgian study estimated the cost-per SRE- (extrapolated to 2010 costs) in patients (2005–2007) with bone metastases secondary to solid tumours (breast, prostate and lung) (Body et al., 2013). The average cost-per SRE- for Prostate cancer, based on the weighted average of inpatient and outpatient costs, was €1,592 for radiation to bone, €3,938 for a vertebral fracture, and €5,125 for a non-vertebral fracture. Costs per patients were €11,092 and €6,382 for surgery to bone and SCC, respectively.

High hospital SRE-treatment costs were also revealed by a small retrospective Portuguese chart review (152 patients from nine hospitals) of costs associated with SRE treatment in breast (n = 121) and prostate (n = 31) cancer patients with bone metastases and ≥1 SRE during the preceding 12 months (Felix et al., 2011). Mean annual SRE treatment cost per patient was similar for breast (€5,963) and Prostate cancer (€5,711). Mean cost per single episode ranged from €1,485 (radiotherapy) to €13,203 (SCC). Early onset of bone metastasis and diagnosis of bone metastases at or after the occurrence of the first SRE were associated with higher SRE treatment costs.

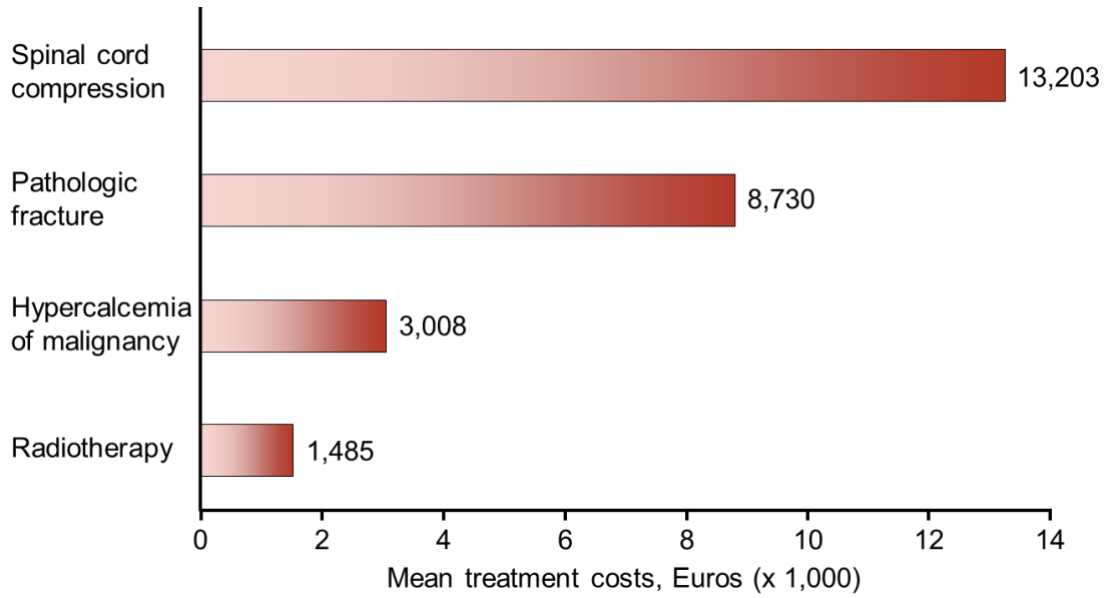

Figure 2.3: Mean treatment cost by Skeletal Related Events type for Portuguese patients with breast or Prostate cancer. (Felix et al., 2011)

2.7 Chapter summary

The health status of prostate cancer patients appears to be lower than the general population norm and health outcomes are poorer in metastatic and prostate cancer patients compared with earlier disease stages. Furthermore, in prostate cancer over half of patients seem to experience pain or discomfort, or problems with mobility or in performing usual activities. While improved HRQoL has been linked to better clinical outcomes in prostate cancer, patients show impairment in most HRQoL domains and HRQoL declines as prostate cancer progresses. The economic burden of prostate cancer is considerable.

The next chapter will discuss how PRO instruments are integrated in prostate cancer research. The focus is on getting the timing right, when to measure outcomes, how to measure it, and ensuring sufficient data points are available for meaningful analyses.

Chapter 3: Integrating Patient Reported Outcome instruments in prostate cancer

3.1 Overview

As noted earlier, the conduct of pharmaceutical research is a conduct of research in a very controlled and regulated environment. There is a whole set of guidance as to how to conduct clinical research according to Good Clinical Practice (GCP) as well as agreed guidelines set out by the International Council for Harmonization (ICH). In addition, the hurdles for achieving regulatory approval and hence marketing authorization is set out by the regulators, mainly the FDA in US, the EMA in Europe and PMDA in Japan. Much of the clinical research design in the pre-approval phase (Phases 0-3) has been driven by these guidelines. This chapter will discuss this guidance, in relation to Patient Reported Outcome (PRO) research, and how this is evolving.

3.2 Regulatory and HTA Bodies and framework for drug development and PRO research

While there is plenty of detailed guidance for the drug development industry when it comes to the conduct of clinical trials through international guidelines and the regulatory agency guidance's issued by the FDA or the EMA, there is much less so from the HTABs. This obviously has been one reason for the skewing of the focus towards the regulatory approval.

The Committee for Medicinal Products for Human use (CHMP), which is part of the scientific committee of the European Medicines Agency (EMEA, who later changed the name to EMA) issued, a Reflection paper on the use of HRQL measures in the evaluation of medicinal products back in 2005 (EMA, 2005). This guidance came into effect as of January 2006. The EMEA guidance was a general guidance on aspects to consider when including PROs in clinical trials, and they stated clearly that they do not provide guidance on how PROs should methodologically be developed. They provided guidance on study design and statistical methods. Specifically, they had recommendations for how to deal with multiplicity and

stressed the importance of PROs in oncology trials. However, PROs were in general seen as "not mandatory" and concerning multiplicity, the use of a hierarchical testing, the PROs were seen as secondary endpoints.

At the same time, the FDA issued a first Draft guidance for Industry on how to proceed with Patient Reported Outcome measures in order to support Medical product development and labelling claims. The FDA in 2009 issued the final guidance, the industry started to take note of how PROs could be integrated into drug development and what methodologies should be used for developing, and validating the PRO instruments (FDA, 2009). The FDA guidance was much more detailed (as opposed to the more general EMA guidance) and more guiding with regards to how to develop a new PRO instrument, starting with an Endpoint Model, a Conceptual Framework and ensuring both content validity and reliability and ability to detect change. The guidance also provided guidance as to considerations for clinical trial design, blinding and randomization, clinical trial quality control and how to handle missing data. Furthermore, it made guidance on statistical considerations and using multiple and composite endpoints.

The HTABs have followed the regulatory guidance from the EMA, the FDA, and very few specific details or guidance has been given apart from providing section heading for inclusion of PRO and HRQoL relevant data in submissions. A more recent development, however, is a collaboration between regulators, namely the EMA and European HTABs. This collaboration has evolved significantly in recent years and facilitated a joint scientific review and advice structures set up by the European network for HTAs (EUnetHTA) and their Joint Action 3 initiative (EUnetHTA, 2013).

Many HTABs will encourage HRQoL data to be included in the application. The German Institute for Quality and efficiency in Health Care (IQWIG) in their Version 5.0 of 10 July 2017 General Method's document includes QoL as an assessment criterion to be used. However, concerning the methodologies, they refer to external guidance from the International Society of Quality of Life (ISOQOL) methods. The EUnetHTA guideline issued in February 2013 (Health-related Quality of life and utility measures) does provide guidance on methodologies

related to use of HRQoL data as part of the endpoint strategy to support the assessment of relative effectiveness of pharmaceuticals (EUnetHTA, 2013).
Furthermore, the FDA recently issued a new Guidance for Patient-Focused Drug Development under the 21st Century Cures Act, (FDA, 2017). This guidance is a significant milestone and very important as it puts the focus of drug development right at the patient. The guidance elevates the relevance and acceptance of HRQoL evidence. The EMA has also issued further guidance for qualification of novel methodologies (EMA, 2013; EMA, 2017). As a result of these changes, recent examples where PRO data has been used to support a regulatory label has been greatly enhanced (EMC, 2018). This means additional evidence and meaningful information is made available to stakeholders, while accepting analyses and methodologies previously discarded by the authorities.

The methodology, or the way the PRO generated information is analysed is key in terms of how useful the information will be to stakeholders. Before 2006-2009, there was little published guidance in terms of standardisation of how the data should be analysed to meet regulators needs. That is not to say there was not a steady evolution of methodologies developed by academic institutions and researchers, but there was no general understanding of how methodologies should be applied to clinical studies and drug development. This lack of guidance improved drastically with the FDA & EMEA guidance in place (Bottomley et al., 2009).

It is with this background the first research paper was written, as a general guidance to the industry on how to conduct clinical research and integrate both the needs of the regulatory agencies as well as the HTABs and ultimately the patients, payers and physicians while providing scientific evidence to support the new drugs developed.

3.3 Study Summary and Critique (Paper 1)

Health economics and outcomes research within drug development. Challenges and opportunities for reimbursement and market access within biopharma research. (vanNooten F, **Holmstrom S**, Green J, Wiklund I, Odeyemi I, Wilcox T). Drug Discovery Today Vol 17, 11/12, June 2012) **http://doi:10.1016/j.drudis.2012.01.021**

The industry, and in particular the clinical team with whom I carried out my Outcomes Research has been struggling to fully comprehend and understand how to conduct patient, payer and HTABs relevant research. Therefore, there was a need to have a relevant publication to refer to, on how to conduct such research. I therefore wrote the paper to have a published reference and framework to help and guide the team on how to think about, and how to structure the relevant Outcomes and Economics research while conducting regulatory clinical studies. The pharmaceutical industry in general has been driven in their clinical research, primarily by meeting the needs of the regulatory agencies as fast, efficiently and effectively as possible. The regulatory, clinical and medical departments therefore drive the research with this in mind. Within these departments, there has thus not been a good understanding of what type of HRQoL and HTABs related research need to be conducted, how to include it, when to perform it, and outright why such research is needed.

The paper built a framework for how to integrate HTABs and payer relevant data collection and data generation into the pharmaceutical development of phase 1-4. There are two dimensions and focus areas that are built into the suggested framework. The first one and the most important one is on the timing of the work. When do you need to start the work? What are the time points for the optimal collection of the data, and what clinical study phase is most suitable for this and for which type of research?

One of the first insights from this research was on the timing of the necessary research should be collected, in other words when should data and evidence be generated and how is data collected? I therefore concluded that much of the work for HTABs and payer relevant output should start in early phase 2, or even earlier in the case where new PRO instruments need to be developed. The most relevant data should be available and ready for dissemination at the time of the regulatory submission. This way, relevant data will be used to support early HTA submissions and payer negotiations.

The second element to consider is which type of research is to be conducted, and what type of data should be collected. We identified three main categories of such research.

1. Firstly, the Patient related research. This is research related to understanding the treatment and disease burden, the signs, symptoms and impacts of the disease on the patient. This insight will then guide the research into specific and adapted PRO instruments, which collect the relevant information in a structured and validated fashion.
2. Secondly, the Disease related research. The focus here is for understanding of the disease, the treatment options, treatment guidance, the epidemiology, disease progression, socio-economic impact and cost consequences point of view.
3. Third and last point is the Payer related research, including economical modelling. This includes understanding the payer environment, the cost drivers, the treatment benefits, the cost of treatment alternatives, cost savings and cost benefits from treatments, which all is built into the economical cost-effectiveness models and budget impact models.

The Figure 3.1 below, extracted from the paper, illustrates the two dimensions of the pharmaceutical drug development and how to integrate HTA/payer related work, including the PRO focused work.

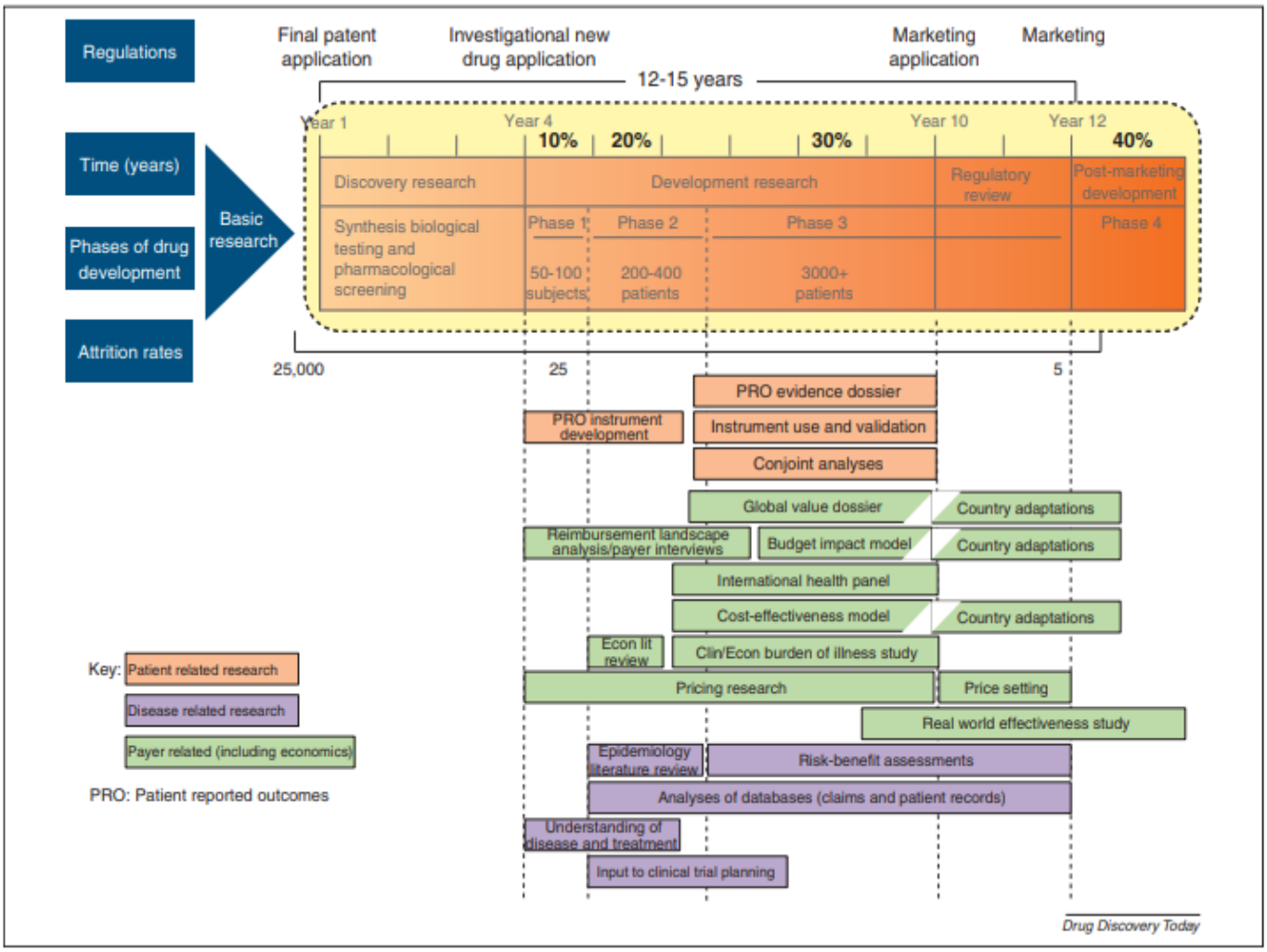

Figure 3.1 extracted from my paper on implementing HEOR in drug development, (van Nooten et al., 2012). The figure illustrates what type and when evidence gathering must be implement in order to ensure the evidence is generated in time for HTA submissions.

The strength of the paper is the simplicity in which the topic is covered. It provides easy to understand and simple guidance to the main activities that must be covered and implemented, when conducting pharmaceutical drug development. There are still relatively few papers providing this type of guidance, which means newcomers in the industry are lacking appropriate guidance through peer-reviewed papers.

Most importantly, the paper provided a helpful reference for my internal audience, in order to help the clinical team understand the basics of Outcomes Research and Pharmacoeconomics of drug research. The paper is still being cited as a general introduction paper for how to conduct HEOR research within the pharma industry, with 27 citations

(Google Scholar (2019) [Accessed on July 21st, 2019]) https://scholar.google.com/, and with over six hundred reads (Research Gate. (2019) Research Gate stats [Online] [Accessed on July 21st, 2019]) http://www.researchgate.net/

In terms of the limitations of the paper, one would be the opposite of the strength; that is, it does not provide specific details as to how to do the research as it focus more on the strategic elements, which are the Patient Related outcomes, Disease related research and Payer related outcomes. It is also difficult to provide very specific guidance without being specific to one disease area or one pharmaceutical compound as more detailed guidance will need to consider treatment specific guidance, general clinical practice and treatment algorithms used in the disease area.

Another limitation is the fact that the focus is primarily on how to deal with implementation within an organization conducting drug development. The equally important part is the external environment and the engagement with HTABs for early dialog. Early Scientific Advice should be part of implementation strategy for new compounds. This point is highlighted in the general conclusion, in section 6.2.1 of my thesis, where I discuss how to build the framework for integration of PROs in pharmaceutical research. More recent papers have also called for a similar type of framework; and addressed internal challenges in implementing HTAB relevant research in pharmaceutical development (Oraiopoulos and Dunlop, 2017).

While the first paper provides an overview of how to conduct the patient centric research, among other HEOR related research, the next paper provides more detailed guidance as to the first step for how to conduct patient interview research. In this paper, the patient takes first stage and dialog is conducted directly with the patients. The benefit from doing this is that patients can report on their signs, symptoms and impacts without a filtering from anyone.

3.4 Study Summary and Critique (Paper 2)

Symptoms and Impact in Non-Metastatic Castration-Resistant Prostate cancer: Qualitative Study Findings. (Tomaszewski E, Moise P, Krupnik R, Downing J, Meyer M, Naidoo S, **Holmstrom S**). Patient, March 2017.

DOI: 10.1007/s40271-017-0227-y

The research question I was requested to reply to from within my clinical team when this research started, was what specific guidance I could provide in terms of PROs and patient relevant endpoints that should be included in future PCa studies, (given that we advance our studies in new disease stages). The priority question for me was to ensure I have conducted qualitative research with patient interviews. As noted in the first chapter, different constraints both in terms of resource availability and in terms of budgetary restrictions meant that the implementation of this research was hampered by these constraints. This qualitative research represents the first ever, that my company, and my clinical team had ever been exposed to. It was hence a substantial effort to get this research off the ground and approved as the concept was new for everybody. However, within the wider community of Outcomes Research such qualitative research is already well established and best-practice guidance is available from the ISPOR working group (Patrick et al. 2011a, b).

As per guidance from the FDA and EMA, any evidence supporting patient centric research should start by understanding the complete patient experience, in other words the picture of the patient signs, symptoms and impacts of the disease. This paper summarises the qualitative study we performed to understand this in the field of prostate cancer. The objective of the study was to develop a conceptual framework for patients in non-metastatic castration-resistant prostate cancer. The conceptual framework is a structure where patient's symptoms and impacts of the disease are mapped out (Patrick et al., 2011a, b).

A literature review was conducted as a search of peer-reviewed literature in PubMed, as well as searching for patient blogs, patient foundations and organizations websites. A first categorization of the signs, symptoms and impacts was created based on these publications. The second step was to conduct semi-structured interviews of clinical experts managing and treating patients with prostate cancer. This included both oncologists as well as urologists.

The concepts identified in the first step literature review were also reviewed and discussed by the study team to confirm the appropriateness of these concepts. The third step, and perhaps the most important one for this type of research, was the conduct of the patient interviews. The interviews followed a semi-structured qualitative Patient Interview Guide, based on the literature and clinician interview input. Patients were asked both open-ended as well as probing questions focusing on symptoms and impacts of living with prostate cancer. Information on frequency, severity, duration and other precipitating factors of symptoms and impacts and how these disturbed their lives was collected. It is important to ensure that all salient symptoms and impacts are captured and thus a saturation table was prepared to ensure all relevant concepts were captured. Saturation is defined as the point where no new unique signs, symptoms or impacts are reported by the patients in the open-ended interview. From the 17 patients interviewed for this study we did unfortunately not reach an absolute saturation, as four new symptoms were still reported in the last interviews. However, as the most salient symptoms and impacts had reached saturation the decision that the conceptual model sufficiently reflected the patient experience in this prostate cancer population was taken.

The study concluded that there were 35 distinct symptoms, which were categorised as urinary, sexual, hormonal, gastrointestinal and other. The symptoms that were most frequently mentioned, as well as had the highest interference rating were erectile dysfunction, loss of libido, urinary urgency, incontinence and hot flashes. In terms of the impacts, the most frequently mentioned were emotional, physical and socio-environmental. The conceptual model created based on the literature and the two interview steps summarises the key signs/symptoms of the disease as well as the immediate and distal impact on the patient.

The Figure 3.2 below, which is extracted from my paper, illustrates the conceptual model.

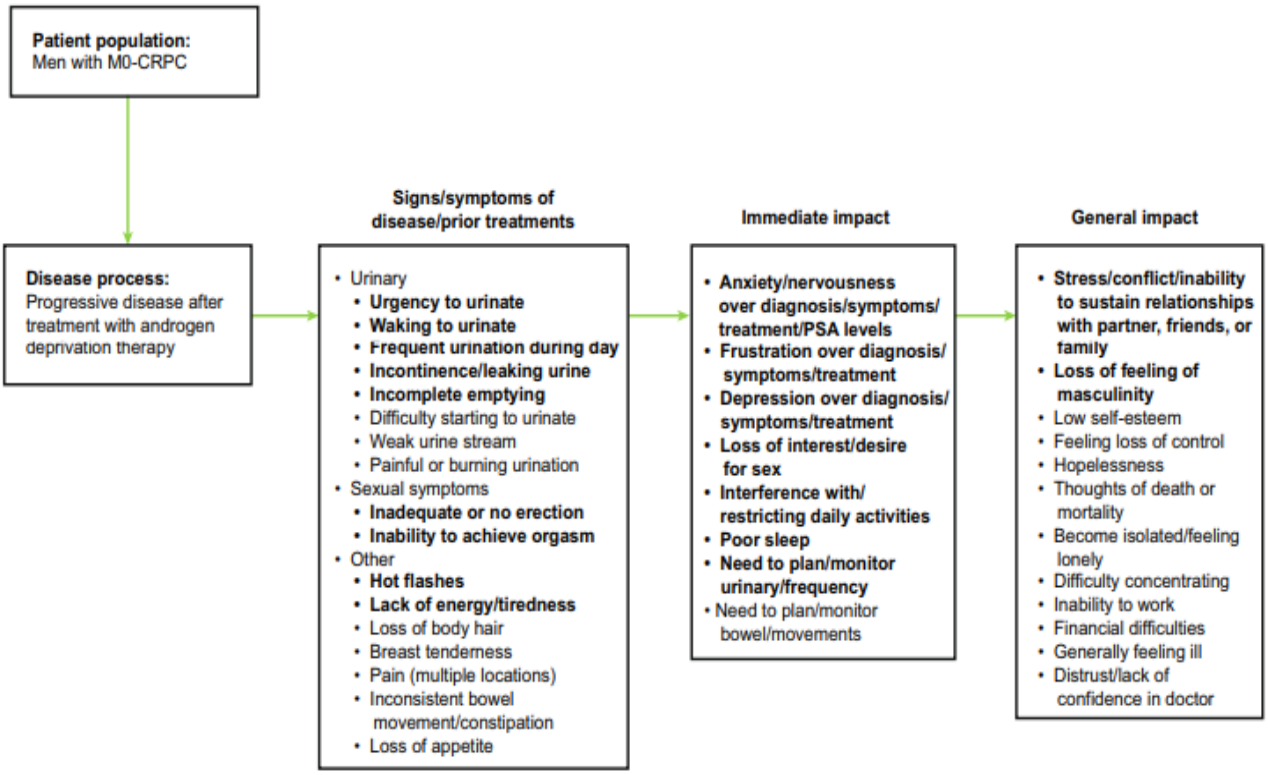

Figure 3.2, from my paper on patient interview (Tomaszewski et al., 2017). This is the conceptual model on prostate cancer that the study documented on signs, symptoms and impacts of prostate cancer.

This research helped in gaining a solid understanding of the how PCa patients feel and how they experience the disease impact; in this new, unknown disease stage. There have been relatively few papers reporting on qualitative research in this prostate cancer patient segment. Both for regulatory approval, and for HTAB negotiations, the paper provides a basis for patient relevant endpoints, linking the outcomes directly to how the patients QoL and how these outcomes can improve their life. Without this link to the patient, it is difficult to confirm that claims and outcomes are relevant to the patient himself and that they have any clinical relevance. This research, and other such patient concept elicitation studies, will also inform treatment guidelines, issued by medical associations, and help anchor them to the patient needs, hence making policies more relevant and adapted to clinical practice.
There are some limitations with the study. One point for discussion is if the patient concept elicitation should be done before the physician interviews. One can argue both ways, as one informs the other. However, the patient concept elicitation is the most pertinent one, as it needs to adequately report on the patient experience, while the physician concept elicitation

will provide a better understanding of how the symptoms and impacts may relate to treatments rather than the disease. This may be a justification for conducting patient interviews first, which we did not do in this paper.

Another point is the fact that patients selected were self-reported as non-metastatic prostate cancer patients. As the patients were selected from a database, access to internet may bias the population. Moreover, the diagnosis in the database is not confirmed by a physician and may be incorrect. The fact that full saturation on the concepts reported was not reached should be noted in future research and if need be modifying the construct of the conceptual model.

As stated in chapter one, a later qualitative research paper (Holmstrom et al., 2018) was undertaken at a time where my company had grown in understanding for this line of research. This enabled me to obtain both appropriate funding for a more thorough research approach, as well as to obtain internal support, especially through discussions with our medical team, which further enhanced the study protocol. Nevertheless, paper 2 contributed at the time with new insights as we constructed the conceptual framework to illustrate the patient experience based on both the physical and emotional domains as well as other impacts such as self-care; many of these had not appropriately been considered when designing clinical studies so far. This paper was most likely to act as a tipping point for the company, for a deeper comprehension of the importance of engaging with the patient, and not only focusing on clinical efficacy and safety aspects. The Outcomes Research I needed to conduct to support enzalutamide would thereafter become easier to obtain approval for and be funded

3.5 Chapter Summary

To support the patient centric research in prostate cancer, two important activities need to take place. Firstly, the clinical studies and the design of the studies need to correspond with the evidence generation needs of the HTABs and the work must be done at an early stage of the clinical study program, usually in phase 2. Secondly, patient interviews need to be conducted early on to ensure a complete picture of the patient's symptom burden and

impacts of the disease and the treatments is available. This will guide much of the patient centric research, the selection of the PROs and protocol design that ensures adequate data collection with meaningful data collection time points and duration that match the disease progression. All of the research needs to be guided by a strategic plan and consider all of the regulatory and HTAB guidelines.

The next chapter will discuss the analyses of PRO data collected in the clinical studies. As instruments have pre-defined analyses algorithms and scoring manuals, all associated with documented validation work and validations documented to show validity of the instrument, most of the papers will follow these pre-defined guidelines. The reported papers report results from scoring guidance.

Chapter 4: Analysing the Prostate Cancer Patient Reported Outcome Instruments

4.1 Overview

The previous chapter provided an outline as to how we create the foundation for understanding patient outcomes, and patient centric research. What type of research is needed and how do we ensure the evidence is collected in the early stages of clinical research? It discussed the importance of reaching out to patients in order to document the signs, the symptoms and the impact on the patient, as derived both from the disease and the treatments. When all of this is correctly executed, the next steps will be analysing the PRO & HRQoL data you have collected.

Most PRO instrument provides pre-defined algorithms on how to calculate and report results and summary scores. This guidance is collated in so called Scoring Manuals. The instrument developer usually develops these at the time of the instrument development. The benefit of these Scoring Manuals is that results can be presented in a way that allows a comparison between studies, as they are performed in a standardised manner. This chapter will discuss how the PRO data from the studies were analysed and reported using these pre-defined guidance's and algorithms.

4.2 Study Summary and Critique (Paper 3)

Effect of enzalutamide on health-related quality of life, pain and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (PREVAIL): results from a randomised, phase 3 trial.
(Loriot Y, Miller K, Sternberg C, Fizazi K, DeBono J, Chowdhury S, Higano C, Noonberg S, **Holmstrom S**, Mansbach H, Perabo F, Phung D, Ivanescu C, Skaltsa K, Beer T, Tombal B).
Lancet Oncology Vol 16 May 2015.
DOI: 10.1016/S1470-2045(15)70113-0

The publication is the first paper where the PRO analyses for enzalutamide, were separated out from the key clinical paper where primary endpoints had been reported. Thus, a separate SAP was constructed for the PRO analyses, with a focus on post-hoc analyses of all PRO instruments included in the study. At this stage of my research it was important to focus the Outcomes Research methodology on an approach that can easily be referenced and justified to the internal clinical team as a validated research method in order to gain acceptance. Therefore, the established scoring algorithms were implemented in our SAP at this point in time.

The publication reports on the HRQoL results from the PCa clinical phase 3 study of PREVAIL. The objective of this paper was to examine the secondary endpoints, as defined in the study protocol. This included change from baseline, percentage improvement and time to deterioration in pain and HRQoL, as well as the proportion of patients with Skeletal-related events.

The study prospectively collected three PROs, the Functional Assessment of Cancer Therapy-Prostate (FACT-P), the EQ-5D and the Brief Pain Inventory (BPI) at several time points, including the baseline values at the start of the study. The improvement or deterioration of the patients HRQoL was measured through these instruments and using pre-defined thresholds. Most PRO instruments will have pre-defined thresholds to indicate which change in score is indicative of a clinically meaningful difference. This threshold is called the Minimally Important Difference (MID), or MCID (minimal clinically important difference). The MID is usually reported with a range and this range can be used to interpret either group differences for a population, or the individual patient. The lower end of the range is used to interpret the group difference, whereas the upper range should be used to interpret the individual patients change because the measurement errors will be larger for an individual patient and thus represent a larger variance.

The time to first HRQoL deterioration was calculated as the time from the date of randomisation to the date of first recorded deterioration. Patients had to complete at least one question at an assessment point in order to fulfil questionnaire compliance. To get an idea on the longitudinal changes of HRQoL, the change from baseline was analysed using a

mixed-effects model for repeated measures, while controlling for baseline covariates. The Mixed-effects models for repeat measures use all data available and assumes that missing observations are at random. However, as it is also possible that missing values are not at random, additional sensitivity analyses were performed using a pattern-mixture model with placebo-based pattern imputation. Both models used data up to week 61.

The results showed that no clinically meaningful decline was observed during the first 25 weeks while on enzalutamide treatment, using the FACT-P total score and the prostate cancer subscale. The placebo arm however showed a higher than MID decline at all visits. The delay in decline in the HRQoL in the enzalutamide arm was confirmed with the sensitivity analyses. Also as measured through the EQ-5D utility index there was a beneficial effect, as well as with the Visual Analog Scale (VAS), as indicated through the change from baseline scores. Looking at the pain, as measured by the BPI, patients had less deterioration with enzalutamide at week 25 as compared to placebo.
The Figure 3.2 below illustrates an extract from the paper on the results of the FACT-P total score and prostate cancer subscale adjusted mean change from baseline.

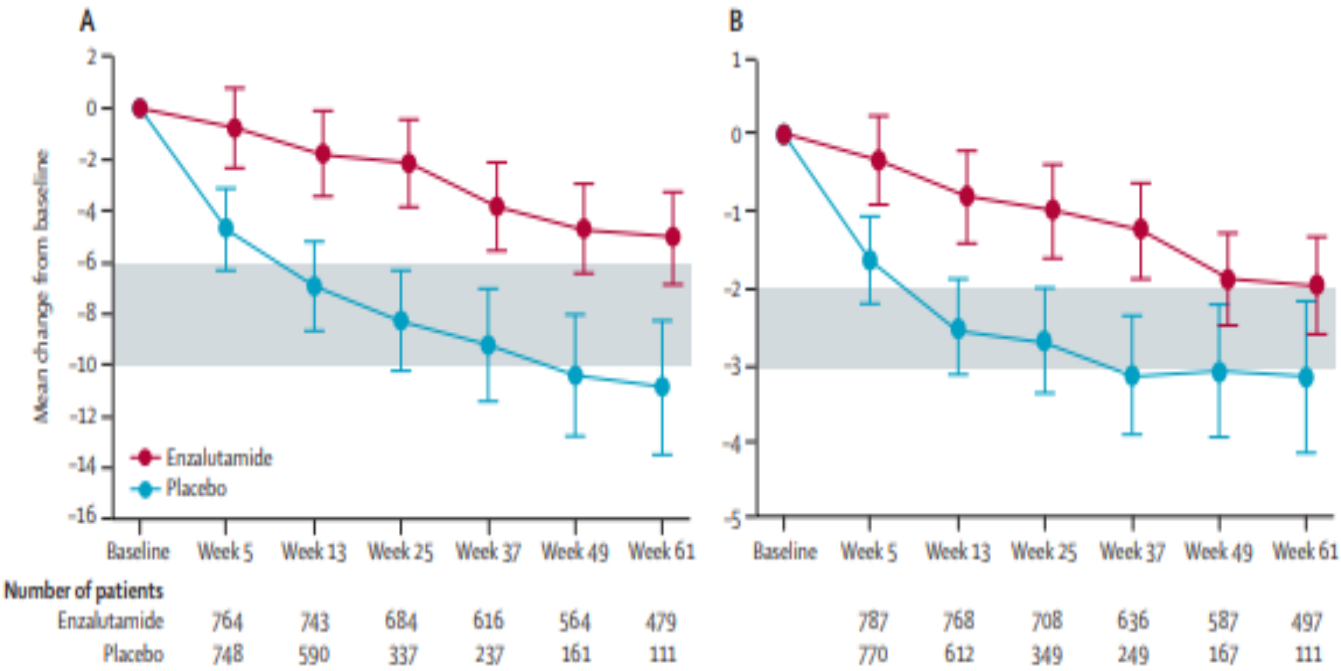

Figure 3.2. Extract illustration from the paper reporting the results over time of FACT-P total scores (graph A), and the Prostate cancer subscale (graph B), with both treatment arms of

enzalutamide and placebo. The grey area of the graph indicates where the difference reaches a clinically meaningful change in the total score (Loriot et al., 2015).

Overall, the paper concluded that there was a significant and clinically meaningful benefit from enzalutamide, as compared to placebo in maintaining HRQoL over time as well as in the time to the first skeletal related event (SRE). We believe this was the first report of EQ-5D responses and SRE assessments in this prostate cancer population. This is also one of the strengths of the paper as new data and information was revealed in this prostate cancer population; making it possible to use the EQ-5D data from this population and make comparisons of QoL assessments in other PCa populations using the same instrument. The paper was also the first where detailed PRO data was reported for enzalutamide with more details than just descriptive statistics. The positive effect over time was well illustrated with the analyses of the FACT-P total scores, clearly showing the positive effect over time with the new treatment, thus supporting a long term QoL effect of enzalutamide.
The paper contributed not only to the overall understanding of the treatment benefit of enzalutamide, but also helped advance the understanding of Outcomes Research and its benefits within the company, and within the medical community for PCa treatments.

The limitations of the study were in particular at the later assessment of week 61; the number of patients was low. For BPI, already at week 25 the number of patients was low. This weakens the results but may be mainly due to disease progression in the placebo group as patient discontinued reporting at that time.
The paper presented the adjusted mean change in FACT-P scores over time. Another way, and one favoured by some regulatory agencies, has been to show results as Cumulative distribution functions (CDF). Handling of missing data can also be done with different methodologies. The next paper addresses this and presents results using CDF, as well as discussing missing data handling methods.

4.3 Study Summary and Critique (Paper 4)

Impact of enzalutamide on quality of life in men with metastatic castration-resistant prostate cancer after chemotherapy: additional analyses from the AFFIRM randomized

clinical trial. (Cella D, Ivanescu C, **Holmstrom S**, Bui C, Spalding J, Fizazi K). Annals of Oncology 26: 179-185, 2015

DOI: 10.1093/annonc/mdu510

This paper reports results from the additional PRO analyses we performed from our AFFIRM clinical phase III trial, a randomized, double-blind, placebo-controlled study in prostate cancer treated with enzalutamide. The conceptual planning of this paper was similar to that of Paper 3 and the clinical team had gained in understanding of the type of research my Outcomes Research team was conducting. Results were available from two of our key clinical phase 3 studies and the knowledge and understanding of the PRO data was positively building up. At the same time, I needed to confirm and document how robust the PRO data was in terms of representing a true clinical benefit, rather than a false signal. This testing was done through different analyses on missing values. Key in my mind, was also always to construct a way to positively illustrate what the PRO data looked like over time, in comparison to placebo treatment. The research also advanced well in terms of providing a relatively rich data source of PRO data from all ongoing and planned future studies the company conducted. The paper therefore focuses on solidifying the strength of the positive signal we saw from both phase 3 studies and ruling out bias due to missing data, while also exploring different ways to visually present our data.

We had noted that regulatory guidance had called for increased collection of PRO data and for expressing the results using different methodologies, such as Cumulative Distribution Function (CDF) plots. This is a way to present the percentage of responders at each score change value and allows at a glance view of the difference between treatment groups. The CDF can visually express all possible score changes rather than a single score, as is the case for responder analyses. I therefore selected to report the CDF plots in this paper as a means of visualising the population benefit of enzalutamide treatment.

PRO data was collected throughout the study using the FACT-P instrument. The FACT-P is a 39-item questionnaire with five subscales for physical, - (PWB), social, - (SWB), emotional, - (EWB) and a functional-wellbeing (FWB), as well as a prostate cancer subscale (PCS). There

are also three indices with a Trial Outcome Index (TOI), a FACT Advanced Prostate Symptom Index (FAPSI) and a Pain-related score (PCS).
Many scores, such as the FACT-P total score has derived a documented Minimally Important Difference (MID) range, which is empirically derived and documented. The MID is a way to express what such a summary score, or total score means when it comes to clinically meaningful change. In other words, when a score surpasses the established MID, one can claim that it has shown a clinically meaningful change that can be relevant for the patient.
The longitudinal analyses on change from baseline on the FACT-P scores were analyses with the so-called Mixed effect Model for Repeat Measures (MMRM). The MMRM assumes that any missing data are missing at random. This is a reasonable assumption, but one cannot be sure that this assumption is valid and thus additional analyses using the Pattern Mixture Model (PMM) were carried out. These address the possibility that the missing data is not at random.

The results from these analyses showed that overall 67.2% of the enzalutamide treated patients and 31.8% of placebo patients had no missing data at all. The treatment discontinuation was the reason for almost all patients dropping out, primarily due to disease progression.
The MMRM analyses for all FACT-P scores were analysed and presented graphically as a mean change from baseline at the different time points of weeks 13, 17, 21 and 25. Using the pre-established MID to express the meaningfulness of these changes we show that all changes in the enzalutamide group were small or within the MID, in other words not clinically meaningful, whereas in the placebo treated patients all scores by week 13 or 17, except for the SWB and the EWB were clinically meaningful.
The PMM analyses confirmed the results from the MMRM analyses, although the difference in change in the enzalutamide treated patients were smaller than in the placebo group after week 25 onwards.

The CDF plots for each score were analysed and showed the same pattern in results with the MMRM/PMM analyses. The distribution functions were favourable to enzalutamide over placebo for the entire range of response levels. The MMRM and the CDF plot is represented below for the analyses of the prostate cancer subscale score.

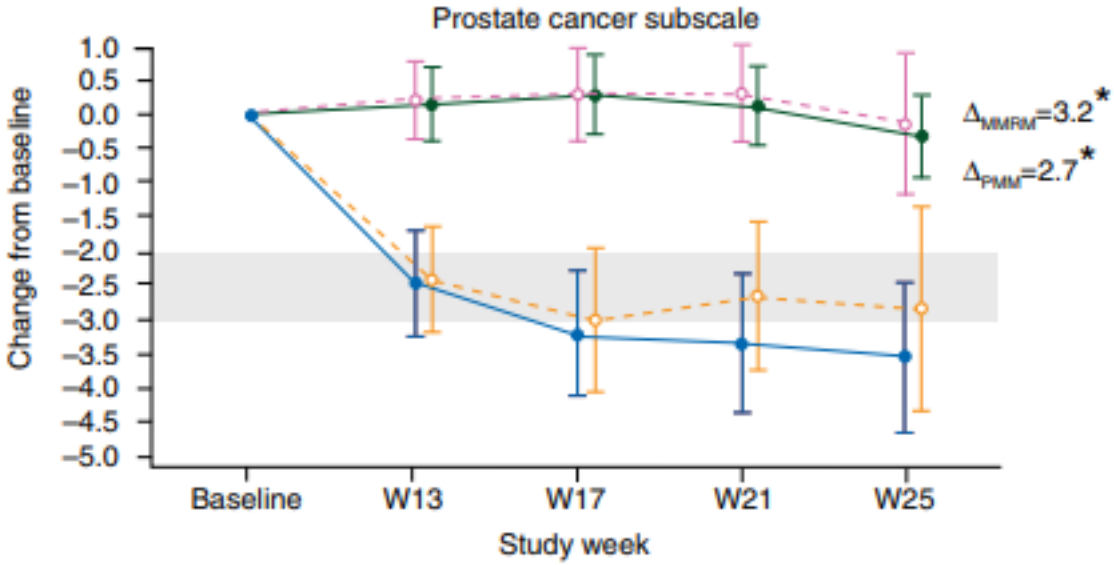

Figure 4.1. Extracted from my paper showing change from baseline for placebo and enzalutamide using the MMRM and PMM analyses. The shaded area represents the MID range on the Prostate cancer subscale score. The solid lines show the MMRM and the dotted lines the PMM analyses. Green and pink are enzalutamide and blue and yellow are placebo responses (Cella et al., 2015: [Figure 1, p183]

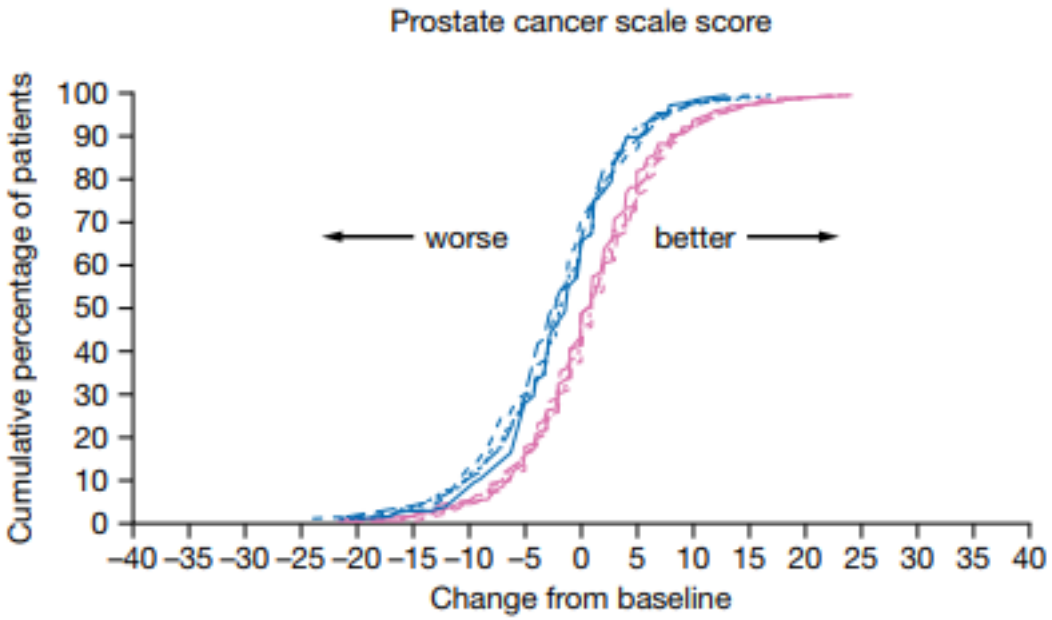

Figure 4.2. Extracted from my paper showing the CDF curve of percentage change of the Prostate cancer subscale score percent change from baseline at each visit. (Cella et al., 2015)

In summary, these analyses and figures show how more detailed analyses further support the improvement in HRQoL of patients treated with enzalutamide, specifically in improvements in pain and the increase in time for HRQoL deterioration observed with enzalutamide over placebo. The MMRM and the CDF graphical representation of the individual score change from baseline is increasing the understanding of the benefit for the patient and guide the patient as to what specific benefit he can expect, such as pain related benefit.

The CDF plots show a clear separation of the curves in favour of enzalutamide and for all FACT-P scores and subscales, except the EWB, PWB and SWB. This helps to understand that the benefit is more marked for disease specific and symptom related measures rather than the general items such as Social or Emotional well-being.

In terms of weakness or limitations with this paper, one can say that the chosen MMRM and PMM statistical methods are one of many that can be selected for analysing longitudinal data and handling missing data. There is however no universally accepted method by the scientific community and thus it is hard to conclude if this is the best method or not. Testing both for missing at random (MMRM), as well as not at random (PMM), and showing that there is no substantial difference in the results, strengthen the overall results of these analyses and confirming the impact of missing data is the same regardless of data missing at random or not.

This paper provides additional methodological approaches, firstly to handle missing data (through the MMRM and PMM) and secondly on graphic representation of results. Handling of missing data is always going to be critical issue in PRO analyses, as this can lead to biased results, and a risk of not being a true representation of the results. The MMRM and PMM analyses are therefore important in support of the true positive treatment outcome of enzalutamide.

Additionally, this paper made use of different graphical illustrations in presenting the results in a format that, at least some of the decision-making bodies and stakeholders are more familiar with. As such it is an important contribution to the evidence supporting decision-making on if, and when, enzalutamide should be used in prostate cancer.

One of the critiques of the paper is the complexity of the MMRM and PMM analyses. As they are not frequently used, the reader may find them difficult to grasp. The paper may have

benefited from further description of the methods to help the reader understand the methods and how this approach compares to other comparable methods on missing data. However, one still missing important piece of evidence, from a payer perspective, as well as from a patient and physician perspective, is how enzalutamide behaves in relation to other available treatments. To address this gap, the next research paper was designed to provide comparative, direct head-to-head data with one of the more frequently used prostate cancer treatments.

4.4 Study Summary and Critique (Paper 5)

Impact of Enzalutamide Compared with Bicalutamide on Quality of Life in Men with Metastatic Castration-resistant Prostate cancer: Additional Analyses from the TERRAIN Randomised Clinical Trial. (Heidenreich A, Chowdhury S, Klotz L, Siemens D, Villers A, Ivanescu C, **Holmstrom S**, Baron B, Wang F, Lin P, Shore N). European Urology, 2017, 534-542. **DOI: dx/doi.org/10.1016/j.eurouro.2016.07.027**

Decision-makers, HTABs, payers and treating physicians make daily decisions in terms of which drug to choose, based on efficacy, safety, possible cost benefits, and increasingly also based on impact on QoL for the patient. It was therefore crucial to have information available on how enzalutamide impacted QoL, as compared to other treatments. This research was in the planning stage already, after the first phase 3 data from PREVAIL was available. There was still an amount of uncertainty with regards to the effect size and how the drug stood up to comparators. A direct head-to-head study was therefore not a high priority for the clinical teams, and it required the team to get the timing right for such a study. However, through internal dialog and persistent focus, I managed to get the research off the ground. In addition, the team agreed that we include many PROs to enhance the clinical results with QoL information and build on the positive results from our previous studies.

PROs included were the FACT-P, EQ-5D and the Brief Pain Inventory (BPI), short form. In addition, the outcomes related endpoint analyses were planned within a separate SAP to secure upfront detailed analysis. This paper reported on the results that corresponded to the outcomes focused SAP, which I conceptually planned in accordance with previous studies and with experience and insight gained from these. The analysis of QoL results focused on the

Enzalutamide study in comparison to the comparator of bicalutamide. Bicalutamide is a so-called second-line hormonal therapy with a well-established efficacy profile in prostate cancer. The lack of direct head-to-head comparative data with enzalutamide versus an active treatment, at the time of this research, was one of the key drivers for conducting this study. Several PRO instruments were included in this study to enable us to obtain, not only efficacy data, but also a direct comparison in terms of effect on HRQoL.

The PRO data was collected throughout the study, with baseline measures, and an assessment every 12 weeks until discontinuation. The pre-defined MID, was obtained for all of the domain scores, the utility scores, and pain scores. The MID is generally expressed as a range. The lower number to interpret change from baseline between and within treatments was used. The upper limit was used for deterioration analyses. Like in the previous paper, we analysed the data using the mixed effects mode for repeated measure (MMRM), assuming that missing data are at random. However, to address the possibility that the data is not missing at random, which could be due to toxicity, disease progression or death, also a second analysis using the Pattern Mixture Model (PMM) was performed.

The results were reported from 375 patients randomised in the study. The median duration of treatment was for enzalutamide 11.7 months, and for bicalutamide 5.8 months. Although there was an over-time decline in all FACT-P domain scores, there was a significant difference in favour of enzalutamide at week 61 in three of the FACT-P domains (EWB, FAPSI-8 and the FACT-P) using the MMRM analyses. The PMM analyses showed seven of the domains to be significant in favour of enzalutamide (FWB, EWB, PC, FAPSI-8, TOI, FACT-G and FACT-P). However, no bicalutamide change from baseline showed a benefit over enzalutamide in any of the domains.

The results from the EQ-5D VAS scores were maintained with both treatments in the MMRM analyses. For the utility score we showed that with enzalutamide, the score was maintained up to week 49, but with bicalutamide, the score deteriorated after week 13 with a clinically meaningful decline. For the pain analyses, with pain at its worst there was a smaller increase in pain at week 61 with enzalutamide as compared to bicalutamide.

A strength of the study is that the results are consistent with those seen in placebo-controlled studies with enzalutamide (Beer et al., 2014, Loriot et al. , 2015) indicating that effect size and treatment benefits are not relative, but true outcomes. This study was also the first one to report on an active treatment comparison and including HRQoL data from the two active arms. Comparative studies with two active treatments in prostate cancer are rarely performed by companies. This paper therefore contributed to the common knowledge of how two active treatments compare, not only in terms of efficacy, but also in terms of impact on HRQoL for the patients. It also provided relevant data to HTABs on how the two drug classes may have a different mechanism of action and therefore cannot be seen as equivalent in the decision-making process.

One can of course comment on the selection of comparator, as bicalutamide is used less and less given that drugs that are more effective are available. However, bicalutamide has long been a well-established treatment and thus provides a good reference for treating physicians in terms of both efficacy, but also in terms of safety and QoL benefits. The HRQoL were however only exploratory and had thus not been included in the analysis hierarchy as key primary or secondary end-points. This can be seen as a clear limitation as it weakens the significance of the outcome, at least statistically speaking. Future studies should consider including HRQoL as at least key secondary endpoints to strengthen the validity of the QoL messages.

The next paper expands into other relevant safety concerns. The skeletal-related events (SRE's) are one of the key concerns in terms of complications for the patient, and potentially an event that has major implications on the patient well-being and QoL.

4.5 Study Summary and Critique (Paper 6)

Skeletal-related events significantly impact health-related quality of life in metastatic castration-resistant prostate cancer: data from PREVAIL and AFFIRM trials. (Saad F, Ivanescu C, Phung D, Loriot Y, Abhyankar S, Beer T, Tombal B, **Holmstrom S**). Prostate Cancer and Prostatic Diseases (2017) 20, 110-116

DOI:10.1038/prostate cancern.2016.62

The paper came about as a collaborative effort between the clinical team and my Outcomes Research team, as both the clinicians need to understand the impact of SREs, as one of the key safety concerns, as well as from an Outcomes Research point of view where SRE's may have a dramatic effect both on HRQoL, as well as the HE modelling. As a result, I established the focus on the HRQoL work stream as a distinct and separate research question. This paper is the result of this research.

While reporting on QoL aspects of prostate treatment it is important to understand what specific items of the HRQoL aspects has the biggest impact in terms of suffering, but also in terms of treatment costs and complexity of the disease progression, and/or with the treatment. The SREs as a safety event, is a summary term used for various skeletal related events. By definition, and for these analyses, the SREs include pathological bone fractures, spinal cord compression, palliative radiation or surgery to the bone as well as change in antineoplastic therapy secondary to bone pain. The SREs may cause decreased mobility, which can lead to loss of independency and thus a related decrease in HRQoL. All of these have been associated with increased mortality in patients with bone metastases (Howard, 2016). This study examined the impact of the SREs on the HRQoL.

The paper reports on the analyses of data collected in the two prostate cancer studies of AFFIRM and PREVAIL where the effect of enzalutamide was measured against placebo. The PRO instruments included in the studies were FACT-P as well as the EQ-5D. The pain was also assessed with the Brief Pain Instrument (BPI). The data was collected at baseline and weeks 5 and 13 and every 12 weeks until discontinuation in the PREVAIL study. For AFFIRM there was data at baseline, week 13, 17, 21 and 25 and thereafter every 12 weeks until progression and discontinuation. To assess the change from baseline the Minimal clinically important difference, or the MID previously established was used.

To establish what the impact of an SRE was on the HRQoL, all the assessments up-to-date of the SRE (any category), and the first post-SRE assessment were included. To evaluate the random effects for each patient trajectory of the HRQoL, a linear mixed-effect model to assess each patient's effect before the first SRE was used. The predicted value of the post SRE

compared with the post-SRE value of the HRQoL was used to calculate the trajectory-adjusted mean change (TMAC). The clinical impact and meaningfulness of the TMAC results were interpreted using the previously mentioned MIDs.

All results were analysed for all SRE data by, a) combined for treatment arms, as well as, b) stratified by treatment arm;

a) Combined for treatment arms:

The results from the PREVAIL study show that using the EQ-5D utility index decline, as calculated with the TAMAC change, the impact of any SRE category had a significant impact on the HRQoL, exceeding the lower limit of the MID range. The highest impact, as measured by the decrease of the utility index can be seen with spinal cord compression. Analysing the FACT-P domains, we can again see that spinal cord compression has the broadest impact with seven of the nine domains significantly diminishing.

In the AFFIRM study 34% of the patients experiencing at least one SRE, with radiation to the bone as the biggest category (24% of patients with at least one SRE). The number of patients and the distribution of the SRE categories were similar in the two studies. Like in the PREVAIL study, a clinically meaningful and statistically significant decline in the FACT-P and FACT-G total scores with any SRE category was seen.

b) Stratified by treatment arm:

The data were analysed for both studies of PREVAIL and AFFIRM stratified by treatment. The results in PREVAIL showed a statistically and clinically meaningful decline in four FACT-P domains (functional well-being, prostate cancer subscale, FACT-P total score and FACT-TOI) in the enzalutamide treated arm after any SRE. In the placebo treated arm, there were no statistically significant declines in FACT-P outcomes, except for the physical well-being. For the AFFIRM study also showed a statistically significant and clinically meaningful decline in FACT-P total score, prostate cancer subscale and FACT-G total scores. Again, no significant change was seen with placebo.

With this study, linking the quantitative PRO measures with the decline in the HRQoL and progression of the disease is done. An association between SREs and the impact of the patients functioning and decline in general of the HRQoL can been shown. As SREs have a significant impact on the patient's functionality and HRQoL, and thus any effect one can have

delaying the onset of SREs will be a desired and good outcome for the patient and treating physician.

One of the strengths with this paper is the fact that two of the enzalutamide studies were combined to look at a larger prostate cancer patient segment, which better reflects the population treating physicians have to deal with in every-day practice and thus provides a more holistic understanding of the effect of SREs. The studies also included several PRO instruments, which were here analysed in terms of association to SREs.

As one PRO may provide sufficient sensitivity in terms of picking up meaningful differences in one domain, this may be the reverse with another instrument. Therefore, for instance, FACT-P did not pick up on an association with pathological bone fractures with any significance, whereas the EQ-5D utility index did pick up such an association. The importance of having multiple PROs, including disease specific instruments, as well as generic health questionnaires, is underscored with these findings.

The EQ-5D has often been described as a relatively blunt instrument, but these findings show that it can sometimes outperform other disease specific instruments, in terms of sensitivity to pick up meaningful changes. This may be an important strength and contribution of this paper. In the bigger picture of this research stream, the paper provided unique and important knowledge on how safety profiles can and will impact, not only on the clinical outcomes, but the relationship of this to the QoL of the patient. This QoL change will also then have an impact on the health economic model as both costs and decreased QoL will influence the cost-effectiveness of the compound. Perhaps equally important is that the paper articulates with more details and granularity on how the disease progression will impact on the patient. This is an important piece of information that can become a part of the dialog between the physician and the patient. Such information will enrich the dialog by providing patient relevant information in the hands of the physician in a format that speaks to the patient with information that he can relate to.

As to limitations of this study, the methodology of using a trajectory-adjusted mean change (TMAC) for our calculations of the impact on HRQoL may not be the easiest to digest. The

audience for this paper may therefore be somewhat limited and we could consider adapting the results and output for a more clinical audience to reach better uptake within the medical community. Also, the decreasing number of patients in the placebo arm will make it difficult to analyse longer-term results. As noted, the analyses by treatment did not pick up the placebo decline in HRQoL, as expected, most likely due to the small numbers. This could therefore be a false conclusion. The data points available for analyses was drive by the study protocol. Therefore, any SREs may have had an earlier onset (time to first SRE) as the period between data collection was not able to determine the exact time of onset. It is therefore difficult to estimate the exact time of onset.

4.6 Chapter Summary

The chapter has provided multiple examples as to how PRO data should be analysed according to the instrument guidelines, expressing the results as summary scores or total scores, such as EQ-5D utility scores, FACT-P total scores and for instance FACT-P Prostate cancer subscale scores. The other important insight from this chapter is to explore different ways of expressing the results and correcting for statistical variability and missing data. This was done through the MMRM, the PMM analyses as well as expressing the results as mean change from baseline, but also cumulative distribution curves, all designed to enhance the way the reader can absorb the rather complex results from HRQoL analyses. The chapter also expanded the horizon into what is important from a patient perspective facing real life challenges, such as “what are my treatment options, what benefits and safety risks do they bring as compared to each other”. Comparative data is thus important, as is the impact on safety and disease progression issues, such as SRE’s.

The wider implication and benefit of these papers is that they help paint a much richer picture of the patient benefits from the enzalutamide treatment in comparison to existing treatment of bicalutamide as well as help understand serious safety and disease progression concerns, such as SRE’s. For HTABs and other decision makers, these papers provide much needed additional granularity and data that help understand the clinical, economical and humanistic implications of this treatment, and as compared to other alternatives. This can

greatly facilitate for instance reimbursement decisions. These data also provide evidence that can support updating of treatment guidance and algorithms, as well as drug policy updates.

In the next chapter, the importance of exploring the inherent richness of the PRO data within the different instruments will become evident. The connection to how PRO data and results relates to hard end-points and clinical outcomes is also important to establish.

Chapter 5: Exploring Alternative Methodologies for PRO Analyses

5.1 Overview

As seen in the previous Chapter 4 and in papers 3, 4 and 5, reporting out on the prostate cancer PRO results and the summary-scores can provide insight into how the patient feel and change over time, and provide insight into how he may benefit from treatment options as compared to placebo or alternative active treatment. Likewise, in paper 6 it is shown that linking key adverse outcomes (SREs) with the effect on HRQoL results is possible and this helps with interpretation of the PRO results as well as can be used to estimate for instance cost-savings. With the summary scores however, it still can be difficult to fully understand the details behind why total scores report out in a certain way, and specifically what drives such change, what domain or symptom makes the patients feel the HRQoL go up, or down.

The research we had conducted so far, and reported on in previous papers, reflected a point in time where we could clearly see a general positive impact from enzalutamide; substantially benefiting the patient through increased QoL, or at least diminishing the deterioration of the QoL. However, even with multiple instruments, which in themselves enabled us to pick up different aspects of the disease progression, we were lacking an in-depth insight as to what exactly is behind the HRQoL benefits. What were the precise benefits that the patients experienced that was driving the overall QoL scores to remain positive? The following research question was therefore formulated through this knowledge and our research now focused on a more deep-dive into the PRO domains and on conducting further item-specific analyses.

5.2 Study Summary and Critique (Paper 7)

Health-related quality of life effects of enzalutamide in patients with metastatic castration-resistant prostate cancer: and in-depth post hoc analysis of EQ-5D data from the PREVAIL trial. (Devlin N, Herdman M, Pavesi M, Phung D, Naidoo S, Beer T, Tombal B, Loriot Y, Ivanescu C, Parli T, Balk T, **Holmstrom S**). Health and Quality of Life Outcomes (2017) 15:130 **DOI:10.1186/s12955-017-0704-y**

This paper reports out the results of in-depth analyses of one of the PRO instruments, the EQ-5D from the PREVAIL study. Additional in-depth analyses are performed, while trying to pick up where the changes are happening, in other words, what domains and symptoms are impacted. The EQ-5D is a generic PRO instrument, as opposed to the disease specific FACT-P for instance. The way the EQ-5D is constructed is that it is composed of five different domains; the Mobility-, Self-care-, Usual Activities-, Pain/Discomfort-, and Anxiety/Depression-domain. Each of the domains will be asking for a three-level input, with 1 as no problem, 2 meaning some problems, and 3 meaning extreme problems. These domains are combined to give a unique so-called health state for each patient. A patient in full health would score a five-digit code of 11111, indicating no problem in any domain. These health states can be converted to a summary score, or EQ-5D index. This is done by applying weights derived from a general population in different countries and gives you the so-called utility index, which is a number from 0-1, where 0 equal a state as bad as death, and 1 equal a state in full health. The instrument also collects the EQ-5D VAS score, which is a straightforward Visual Analog Scale of 0-100, with 0 meaning worse imaginable health state and 100 meaning the best imaginable health state. Few studies with prostate cancer patients have included the EQ-5D instrument and none has previously reported out EQ-5D results in this disease segment of chemo-naïve prostate cancer patients. The EQ-5D data was obtained at baseline, week 13, and every 12-week until discontinuation or disease progression. Data only until week 61 were analysed due to reduced sample size after this.

The change on individual dimensions, time-to-event analyses, as well as the Paretian classification of Health Change (PCHC) were analysed. All of the EQ-5D dimensions were summarized for the proportion of patients reporting either no change, some change, or extreme problems. The PCHC analyses look at the EQ-5D health state and is classified as either “better”, “worse”, or as “mixed”. The proportion of patients with an index score of full health (a score of 1) was also analysed. The time-to-event analyses were used to estimate the benefit of enzalutamide versus placebo with the effect of delaying or preventing deterioration of the patient’s health. Patients who had full health, in other words a health state of 11111 at baseline was used to assess time to worsening.

The results from the individual dimension analyses show a significant effect of enzalutamide in the between-group difference for the Pain/Discomfort dimension to week 37, as well as for the Anxiety/Depression dimensions at week 13 and for Usual Activities dimension at week 25. For the patients with full health (index value of 1), there was a clear tendency for enzalutamide to show greater proportion of patients remaining in health stake 11111 up to week 37, although statistical significance was only seen at week 13 (see Figure 5.1 below).
In the PCHC analyses, we showed that a greater proportion of patients reported improvements on enzalutamide than on those on placebo. The between group differences were statistically significant at weeks 13, 25 and 49 (see Table 5.1 below)
The time-to-event analyses showed a statistically superior result with enzalutamide over placebo in most dimensions. This included divergence from full health, time to decrease of the EQ-5D index or VAS, time to deterioration of Self-care, Pain/Discomfort and Anxiety/Depression.

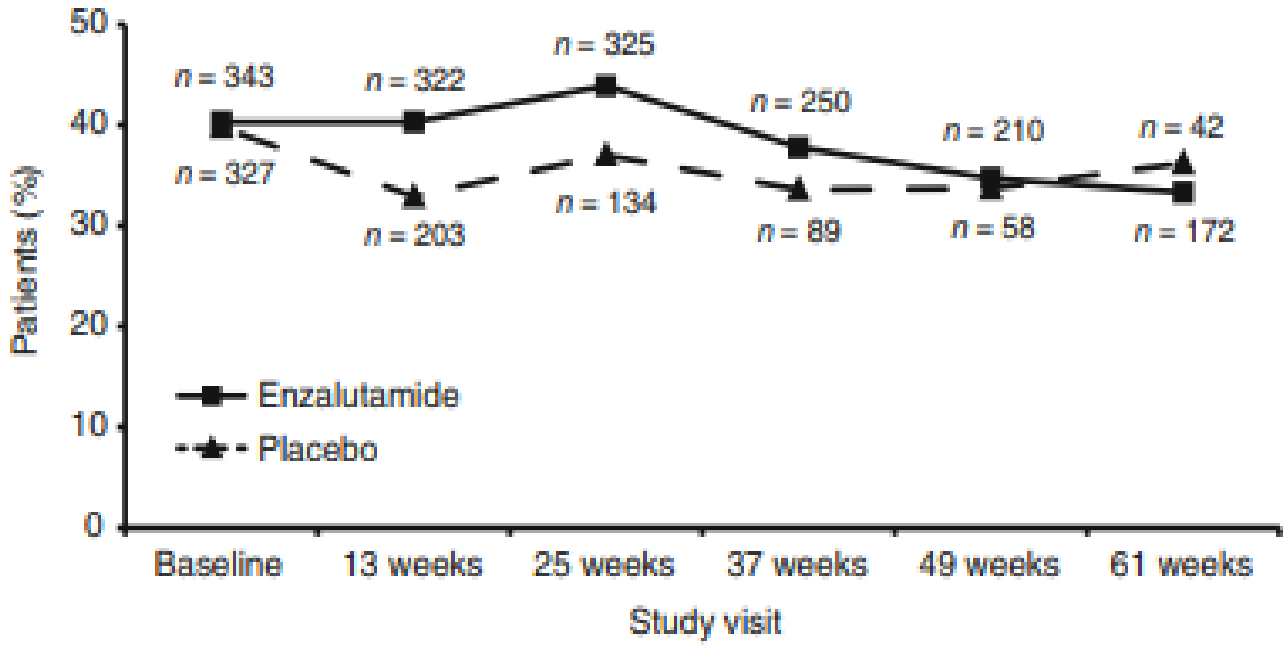

Figure 5.1 from my paper (Devlin et al., 2017), page 6. Proportion of patients in full health, reporting an EQ-5D state of 11111 (full health) as expressed over time during different visits

Table 5.1 show the Pareto classification of health change classification of changes from baseline in EQ-5D dimensions

	Enzalutamide (n=872),	Placebo (n=845),	P value

	n (%)	n (%)	
Week 13	n=783 (89.8%)	n=605 (71.6%)	
Worsening	208 (26.6%)	230 (38.0%)	<0.0001
No Change	337 (43.0%)	242 (40.0%)	
Improvement	190 (24.3%)	94 (15.5%)	<0.0001
Mixed change	48 (6.1%)	39 (6.5%)	

Extracted from my paper (Devlin et al., 2017), page 6, and shows the week 13 results

The paper is able to expand the understanding of the previously reported PREVAIL results showing a significant prolongation of enzalutamide time to deterioration of the EQ-5D index and VAS score, while helping to understand what was driving the changes. For instance, while using the PCHC approach, one can show a considerable movement between levels of pain and discomfort in level of patients improving, respectively worsening. In conclusion, there is a significant HRQoL benefit from enzalutamide and that this is largely driven by changes in Pain/Discomfort and Anxiety/Depression.

These findings are completely new and revealing in terms of providing further in-depth understanding of the effect of enzalutamide and the impact it has on patients. The findings also confirmed our thinking that there are some domains and items and outcomes that are more affected by the benefit of enzalutamide than other ones. Furthermore, the insight obtained from these EQ-5D analyses, provides new ways of analysing and using the data obtained with the EQ-5D instrument. From an academic point of view it helps move the understanding of the EQ-5D, as a generic instrument, well beyond the much-reported utility index, or the VAS score. This paper is also the first paper reporting in-depth results from a generic PRO instrument in this prostate cancer segment. The paper thus highlights, again, the need for both generic as well disease specific PROs to be included in clinical studies, as previously unknown information can be found and disseminated through these analyses. The analyses of the EQ-5D dimensions helped understand previously reported summary scores (Loriot et al., 2015) by exploring and pointing to specific symptoms and disease items that may be driving the changes in the summary scores.

This paper tremendously advanced our understanding of the specific symptoms that most likely were manifesting themselves in the improvements of the total PRO scores after enzalutamide treatment. Subsequently we proceeded with item-specific analysis of all other PRO instruments to complement these findings. However, this research was ground-breaking for us in terms of finally being able to articulate specific impacts on symptoms on the benefit of enzalutamide, something that we had not been able to do before. It is a lot more meaningful to speak to a patient, or a physician about impact on the specific items of self-care, or on pain, than to say that an overall benefit on QoL is a documented with enzalutamide treatment.

The PRO instruments are originally constructed through careful consideration and inclusion of symptom items and domains that are relevant for the patient. Therefore, a lot of relevant disease information on how the patient feel and function is captured. Reporting out the results from these through complex algorithms can however hide some of the information and cloud the understanding of the results. The paper thus highlights the need to fully explore all of the intrinsic data captured by the instrument. In addition, from an ethical point of view, colleting PRO data from patients is undoubtedly some burden for the patient. Thus, to not fully explore and understand the PRO data collected is a waste of time and resources and can be a missed opportunity to understand the benefits the patients have reported on in the PROs.

As to the limitations of the study, the relatively unknown methodologies used, like the Pareto classification, not frequently seen with PRO analyses; thus it may be difficult to understand for some readers. The acceptance and understanding of the methodology will benefit from further studies being published using these methods. Furthermore, the numbers of patients over time was declining due to disease progression. This will make the robustness of the results at the later visits less strong. Another weakness is also the lack of data after disease progression. Ideally, one would need to fully show both high number of patients throughout the treatment visits, as well as link the results to the outcomes once new treatments are initiated. This would provide a full picture of the HRQoL progression.

The next and last paper expands the understanding of the PRO and HRQoL data, and the relationship to clinical endpoints. If we can show that there is a link and association between

how the PROs behave in translating the patient's disease progression with clinical hard-endpoints, then there will be a prognostic value within the PROs and maybe in the future we will be able to replace clinical assessments and tests with PROs.

5.3 Study Summary and Critique (Paper 8)

The association between health-related quality-of-life scores and clinical outcomes in metastatic castration-resistant prostate cancer patients: Exploratory analyses of AFFIRM and PREVAIL studies. (Beer T, Miller K, Tombal B, Cella D, Phung D, **Holmstrom S**, Ivanescu C, Skaltsa K, Naidoo S). European Journal of Cancer 87 (2017)
DOI:10.1016/j.ejca.2017.09.035

At this stage research on enzalutamide had moved ahead quite substantially from when we had started this research, in terms of understanding our compound; and how to plan, implement, conduct and report on our Outcomes Research. I had by now, a good understanding of the impact of enzalutamide on the QoL and, indeed even how the benefit of the drug manifested itself, through which domains. As a final part of this research journey, one of the challenges was related to communication; and how to best make PRO results and Outcomes Research more meaningful to our primary stakeholders such as the treating physicians and the patient. The research question was therefore to see if I could link clinical endpoints with PRO results and QoL data. Could I correlate the Outcomes measures in any meaningful way with clinical outcomes and was there a clear correlation with positive PRO outcomes with clinical endpoint improvements?
The previous papers, numbers 3-7 were exploring different approaches and how data can be analysed, and how the data can be presented in different ways to make it more meaningful to stakeholders. This paper takes one additional step linking the PRO outcomes and results with clinical endpoints, given that the changes in HRQoL is an important determinant of the value of cancer treatments.

Traditional clinical endpoints of Overall survival (OS) and radiographic progression-free survival (rPFS) are well understood and valued by clinicians. The Prostate Cancer Working Group (PCCTWG3) has recommended evaluating any change in individual outcomes, such as the PRO measures, with longer-term outcomes, such as the OS or rPFS (Scher et al., 2016).

Indeed, there has been reports where the association between an improvement in HRQoL and the improvement in clinical outcomes has been shown (Gupta, 2013, Sullivan et al., 2007). However, the relationship between the clinical outcome measure, such as OS and rPFS and that of the outcome of HRQoL is limited. This makes it difficult for clinicians to relate to PRO results, or fully comprehend the implications of PRO data.

This paper used data from the PREVAIL and AFFIRM trials, where patients were treated with enzalutamide for prostate cancer. For these analyses, the FACT-P instrument results were used. All of the FACT-P summary scores and domain scores were analysed. The analyses were done to investigate the relationship between the OS and rPFS and all of the HRQoL measures. In total, all FACT-P data and all domains were used for the analyses. The analyses were done using Cox proportional hazard models with baseline or time-dependent covariates fitted to time-to-event data on OS and rPFS separately. The hazard ratio (HR) with associated confidence intervals (CI) of 95% for the HRQoL variables were used as the key measure. This was calculated as the hazard of rPFS or OS per minimally important difference (MID) score change in the HRQoL variable.

The results from the univariate analyses from both studies AFFIRM and PREVAIL showed a clear association between baseline HRQoL and the clinical endpoints of survival (OS) and rPFS. The multivariate analyses from AFFIRM baseline HRQoL for rPFS was associated with the FACT-P total, FACT-G total, the TOI and the EWB as prognostic factor of rPFS with a (HR; 0.92-0.95). In addition, for OS, the HRQoL values were of prognostic value, with higher values reducing risk of death by 6-17%. Similar association of HRQoL changes over time and OS were shown, with all FACT-P domains associated with OS (HR; 0.75-1.15). In addition, for rPFS the results show FACT-P domains (except FWB, EWB and PCS) to be prognostic of rPFS (HR; 0.86-1.07).

For the PREVAIL study, somewhat similar results can be seen. In general, the point estimates for HRs are smaller in the time-dependent model as compared to the model with the baseline values only. Figure 5.2 extracted from the paper shows the association between longitudinal HRQoL and rPFS (A) and OS(B) in a multivariate model from the PREVAIL data. This is indicative of the type of analyses and results from this study.

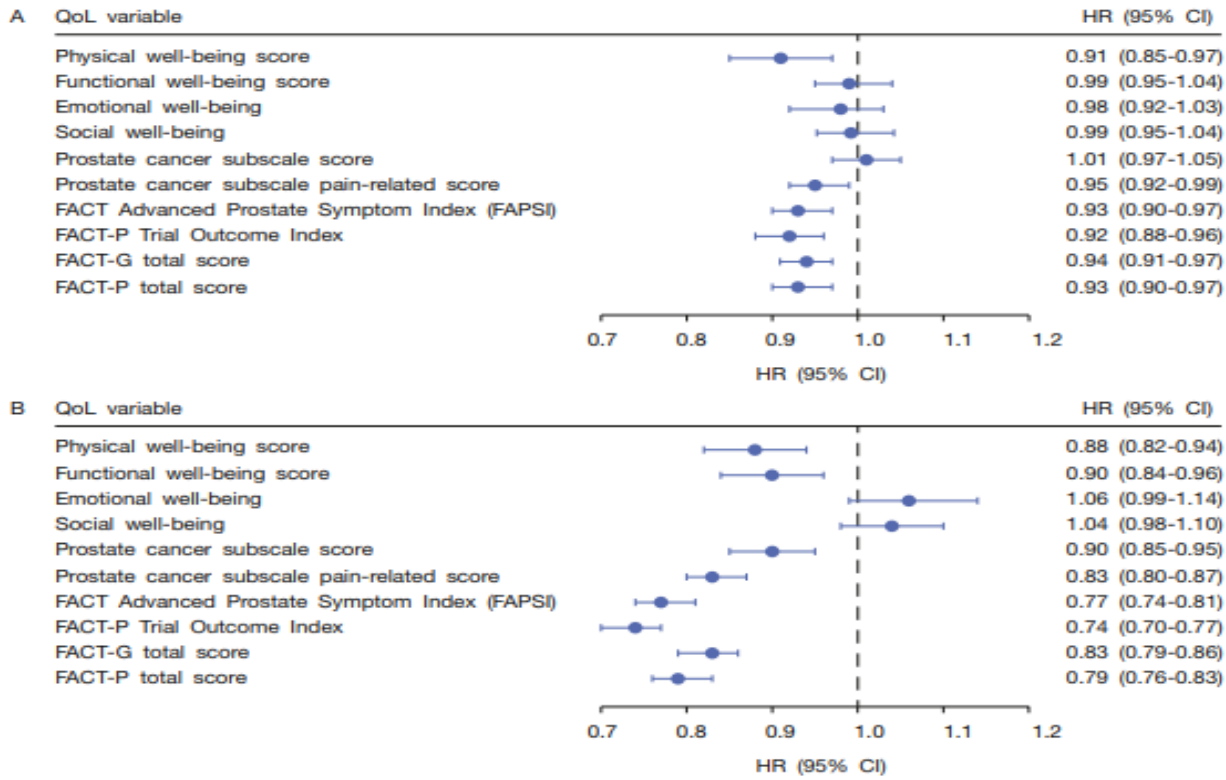

Figure 5.2. Extract from this paper showing the results of longitudinal multivariate analyses of the PREVAIL study on the association between HRQoL and rPFS and OS. (Beer et al., 2017)

This study analysed the data from two enzalutamide studies and explored the association of survival (OS) outcomes with both baseline and longitudinal HRQoL scores. The results indicate that there is indeed a correlation between the HRQoL, both for baseline values as well as for the over-time values for both rPFS and OS in the patients with prostate cancer. The PRO data can therefore be informative in decision-making and influence the physician's treatment approaches as well as help better understand the progression of the disease.

As there are relatively few papers showing the link between PRO results and clinical outcomes, this paper helps advance the science on this front. The relationship with baseline values of PROs in PCa has been reported, but few studies can be found where the longitudinal prognostic value of HRQoL in PCa is explored (Traina et al., 2015). My paper therefore contributed to the understanding not only of enzalutamide in this context, but also to the use of PROs as a predictive outcome of in PCa in general. Combining two enzalutamide studies provided a larger population, providing a good number of data points of both PRO and clinical

data. Both baseline and time-dependent variables were used which expands from other similar papers, where focus was on baseline or pre-treatment data.

There is a clear need for physicians to better understand how to read, understand and relate to PRO results in their day-to-day clinical practice. These two papers (paper #7 and #8) help, first by extracting explicit information about the patient functioning on a symptom-item level. Secondly, by providing the link of the PRO results with clinical assessments and outcomes. This will greatly enhance the way physicians can relate to what the PRO data tells them. Collecting PRO data from the patients is a relatively low-cost and low-burden exercise, as compared to expensive clinical tests and analyses such as scans and laboratory testing. If PRO data is able to capture disease progression as rapidly as an expensive clinical test, then implementing PRO data collection in routine clinical practice can be highly cost-effective and effective way to manage the patient care, and at a much lower cost.

One of the limitations of this study is the post-hoc nature of the analyses, which of course is the nature of such exploratory work. In addition, in terms of the predictive model, other more sophisticated models could be considered, but for investigating the association between the HRQoL domains and survival and disease progressing, this is deemed sufficient. There is however the probability that this is a false conclusion. Further studies are also recommended to validate the findings and associations we found.

5.4 Chapter summary

The chapter is a summary of perhaps the most important papers that I published. Firstly, it provides an example, based on all previous research we had conducted, for how by undertaking further analysis, focusing on specific items within the PRO instruments, we were able to extract much more and more relevant information about the treatment benefit. Subsequently I conducted item-analyses on all of our PRO instruments to gain a much richer picture of the patient benefit, one which we can articulate through publications and other educational material. Through this research I managed to open up a whole new dimension of meaningful information on patient relevant outcomes that was not there before. The EQ-5D instrument here serve as one example of how the construct of the PRO instruments can be

rather complex and results presented in total scores that are difficult to interpret. When the individual items are in the focus, trend and longitudinal analyses can provide enormous insight. This helps stakeholders find the underlying cause of the issues, from the perspective of the patient, and thus can make more informed decisions on what treatments offer and differentiate between treatments.

Furthermore, with my research, I managed to make the important link between clinical outcomes of PFS and OS over time, something that has not been widely reported before. Some papers have indeed made the correlation of PROs as predictive of baseline values for PFS and OS, but not beyond that. The contribution of these findings is therefore quite significant. The ultimate goal may be to get PROs to become part of the every-day decision making for physicians; potentially replacing some clinical assessments, which are often more expensive and much more time consuming. If the PRO trend can indeed predict disease progression, or OS outcomes, this can be used as a simple mean to modify ongoing treatments or predict complications, eventually saving time, resources and money for health care providers. This paper therefore was a culmination of the research I conducted, as the impacts of our results has the potential to change clinical practice.

Chapter 6: Summary, Recommendations and Conclusion

6.1 Summary

The aim of the thesis was to demonstrate and discuss how the use of PRO data in pharmaceutical drug development can enhance the understanding of prostate cancer during the disease progression. The PRO data can reduce uncertainty in decision-making and improve patient care. Such data will help to enhance our understanding of our drugs, thus enable companies to prepare better for reimbursement and market access negotiations as patient specific benefits can be better articulated. The evidence must be generated during the drug development process and be available for HTAB submission. The thesis also discussed how industry currently conduct prospective and retrospective PRO analyses and provide examples of how these can be focused to a more targeted, fit-for-purpose research, eventually better meeting the needs of stakeholders. The pharmaceutical industry should become more familiar with the concept of patient-centricity and take patient-centeredness to heart within the organization in order to meet these demands.

The field of PRO, HRQoL and Patient-centric research is rapidly evolving. Recent changes in the mind-set of regulatory agencies has opened up more opportunities to include PRO related information into regulatory submissions and perhaps provides opportunities for HRQoL information to be used more extensively in decision making. This can be seen for instance in the EMA Strategic reflection outline for 2025, where one of the five strategic goals for regulatory science is to ensure patient-centred access to medicines is advanced (EMA, 2019). Specifically, EMA brings forth the use of PROs and the need to further update guidelines on use of PROs in terms of study design and analyses of the date (EMA, 2019).

Likewise, HTABs are expanding the expectations for new drugs and expect QoL related information. New treatments must not only provide an improvement of the efficacy and safety of drug treatments, but also providing patient relevant improvements in QoL, while still being cost-effective. The industry has sometimes paid a high price, as drugs have had to be withdrawn from the market due to lack of appropriate evidence to support their products. Such was the case for instance with Exubera® where the need of the patients and payers had

not been appropriately catered for, even with a more than USD 2 billion research investment, the drug failed to meet the expectations of the stakeholders and eventually withdrawn (Oraiopoulos and Dunlop, 2017).

The PRO and HRQoL focus of the eight papers have contributed to the understanding and help explain the benefit of enzalutamide in the treatment of PCa. The papers provide, new and ground-breaking information or evidence, in addition to the clinical papers, which report more traditionally on the primary endpoints. As PCa gets more treatments options, it is important to understand and distinguish between the treatments. The QoL aspects are an important part of this understanding.

6.2 Contribution of Research to Knowledge and Implications of the Thesis

Specific key contributions from the research that I, and my research team, conducted have included expanded learning on how enzalutamide impacts patients' lives. The iterative learning from the conduct of one research paper after the other, collectively created a whole new framework for how Outcomes Research can more effectively be implemented within drug development. My personal learning has been steep, at least on a conceptual level, where I have gained insight and understanding on how to position and execute research in front of critical internal reviews; and additionally in terms of the trial and error on how PRO research can best be planned, implemented and how to best construct the analyses plans (SAPs). In general, and perhaps most importantly, I have learnt how Outcomes Research can be introduced as a fairly unknown topic into the public domain while publishing papers on our results. Thus, the collection of these publications, coupled with my personal research journey of learning has enabled me to use the papers as the building blocks for the framework that I present here at the end of this chapter (see Table 6.1)

Prostate cancer as a disease provides a formidable challenge to society and health-care providers in terms of humanistic suffering, burden of disease for the patient, burden for the caregivers and contributes to the increasing health-care costs. At the same time, new treatments are made available at a rapid pace and the drug development focus of these new treatment modalities must secure adequate evidence to support the best use of these treatments and help direct and secure funding to the best available options. While the thesis

makes use and reports on well-received papers by the medical community, as evidenced by comments from the journal editors, on how PROs and HRQoL can be presented, these same papers may not always be adequate, or the most appropriate to address a different stakeholder community, such as HTABs, payers and patients (Fallowfield et al., 2016; Porter et al., 2016).

Methodologically PRO developers are bound by strict criteria to ensure the PRO instruments measure meaningful signs and symptoms, while also ensuring they are able to pick up change and do it consistently throughout populations. Standardized methods are also required to report the results from these instruments so that results can be compared between studies (Patrick et al., 2011a, b). While this is scientifically the only accepted approach in the conduct of such research so far, one also need to provide insight to the burden of the disease, and to the impact, drug treatments have on the patients in a meaningful and understandable format. With the initiatives of EMA and the FDA, as well as some of the HTABs, the direction of the PRO research is now focusing on not only domain analyses, but also item analyses and psychometric and exploratory analyses to fully be able to understand what is truly driving the change in the patient's reported quality of life (EMA, 2016; FDA, 2017).

The thesis advances the understanding of how Enzalutamide works and enhances the QoL of prostate cancer. With Paper 1 and 2 the foundation of understanding prostate cancer and the impact of the disease was set, at least in one of the patient segments of PCa (van Nooten et al., 2012; Tomaszewski et al., 2017). Building on this, Papers 3, 4, 5 and 7 provided new and sometimes unique data of how we can measure the patient progression, using PRO data to illustrate this (Loriot et al., 2015; Cella et al., 2015; Heidenreich et al., 2017). Such was for instance the reporting of the EQ-5D data that had not been reported before in the PCa segment (Devlin et al., 2017). Collectively these papers have helped tremendously to articulate the effect of and advance the understanding of the benefit of Enzalutamide on PCa patients.

6.2.1 A Framework for integration of PRO research within drug development

Extrapolating from these approaches, methodologies and reporting practices, one of the key contributions of the thesis is that it creates a framework for how to integrate PRO research

into pharmaceutical drug development. It provides examples for how to analyse and report the results from PRO research and how to explore the intrinsic value of the PRO data through item analyses of the instrument. Another key contribution is also in providing evidence of the linking of PRO outcomes to clinical endpoints, such as Survival benefit (OS) (Beer et al., 2017)

As a consequence, the PRO results must be reported and presented using methodologies and output as required by the individual instruments, but data should also be explored beyond these and with different methodologies. The papers in this thesis reports on both of these methods. It includes also the conduct of longitudinal change from baseline analyses, conduct of sensitivity analyses and estimating the impact of missing data, for instance with MMRM and PMM analyses and expressing results with CDF plots as in Paper 4 (Cella et al., 2015). Understanding what the most relevant safety concerns are is also important, both from an impact point of view, but also from a cost-consequence point of view, as reported in the Paper 6 on enzalutamide and SRE's (Saad et al., 2017). Equally important is that we encourage the industry to conduct further in-depth analyses and break out of the pre-set mould of how data is analysed and used. This was done in the Paper 7 on how data can be analysed differently, in this case with the EQ-5D instrument (Devlin et al., 2017). This will provide evidence that allows the physician and the patient to have a meaningful dialog on how the drug affects the disease symptoms, what options are the best for the individual patient, and what improvements can be expected over other treatments (Heidenreich et al., 2017, Beer et al., 2017).

The research which has been presented in this thesis and the collective learning from this has enabled me to synthesise this into a meaningful output, in terms of how clinical research perhaps should be conducted, I have created a type of best-practice framework for this type of research. The framework is thus a collection of both the iterative learning, which was possible thanks to the continued research with the same compound for several years, alongside the intellectual learning related to having conducted this research. This has enabled learning about the biggest hurdles and pushbacks within the pharma companies. Each of the papers contribute individually to the framework by providing examples of how that step of the research can be conducted, while also serving the purpose of informing stakeholders.

Table 6.1 A Framework for integration of Outcomes Research within drug development

	Task	Paper contribution
1	Preparation of prospective PRO strategy	1
2	Engagement with authorities (regulators and HTABs) for early scientific dialog and alignment on data needs and relevance of these in the minds of authorities	1
3	Conduct of Patient qualitative and quantitative research. Ensure adequate perspective of patient is documented for signs, symptoms and impacts of disease and treatments	1 2
4	Securing the integration of Outcomes Research relevant endpoints into clinical trial program from early phase onwards	1, 2, 3
5	Conduct of PRO analyses	
5a	Following validated scoring manuals and guidance for individual instruments	3, 4, 5, 6
5b	Conduct of exploratory analyses, such as item analyses on [patient] relevant domains	2, 7
5c	Conduct analyses on correlation between PRO outcomes and clinically relevant endpoints and outcomes	8
6	Articulate results from PRO data in simple, meaningful ways to enable value messages relevant for regulators, payers, HTABs, physicians and patients	2, 3, 4. 5, 6, 7, 8

I believe this framework provides a relevant, patient-centred approach that adequately reports out the evidence to all stakeholders. Decision makers can get clear, easy-to-understand data that will reduce uncertainty in their decision-making. Health outcomes can therefore be optimized, and treatments directed towards the options that best fit the patients need, reduce cost and unwanted suffering. PRO data should be used in daily practice to help guide physicians in patient care. If sufficiently strong evidence is obtained in linking the PRO outcomes with well-established hard clinical endpoints, such as OS, then they can become a highly cost-effective replacement of clinical measures. Ultimately such practice can become an integrate part of health policies and best practice guidance for how to treat PCa,

ultimately saving cost and help advance medical practice. The introduction of such updated treatment guidance may advance the use of patient relevant QoL data and help facilitate and enhance the dialog between the patient and the physician.

6.3 Limitations of the Thesis

There are some limitations of the current thesis. As stated in the introduction, due to the nature of the research within drug development, and where my colleagues and clinical team were when the research started, the only true focus of my Outcomes Research has been through the means of PROs and integration of PROs. Patient centricity is much more than PROs alone, and much more work could be done in understanding the patient experience while they are going through the journey of their disease progression.

Another limitation is the lack of prospective overall analysis plan for how to conduct the Outcomes Research and statistical analyses for the PRO data. A prospective, over-arching analysis plan would help to establish the value of such Outcomes Research in the minds of the clinical team and internal stakeholders, and by doing this, the acceptance of the Outcomes strategy would be established, and could become part of the *a priori* testing hypotheses of the clinical research program. Due to various constraints and concerns, most of the PRO analyses conducted were either exploratory in the statistical hypothesis plan or done as post-hoc analyses. This may reflect a lack in confidence in how well the PRO instruments may pick up meaningful change, or for fear of lack of statistical power to allow PRO analyses to take a key primary or secondary position. As many new papers are now reporting out on the enzalutamide PRO results, confidence in how this type of evidence can be used to inform external stakeholders is building up and further acceptance of the PRO is as part of the statistical hierarchy is growing.

Another limitation is the definition of MID's for each and one of the PROs reported. As MID's are one of the more widely accepted methodologies for expressing what change from baseline is reaching a level of improvement, or deterioration, and that can be classified as clinically meaningful, the definition of what those MID limits are is of high relevance. For the publications used in the thesis, available, published MID's were used. However, the validation methods for how the MID's were established are not always well documented, and for some

of the PRO is used, there is no pre-defined MID's, like for instance for the PR-25 questionnaire. For some HTABs, this is a very important point and they have published guidance on how MID's are used to establish clinical relevance of the PRO results. Thus, only by providing solid evidence on how the MID's are derived and how improvements can be observed, as a change over the MID threshold, will the data be considered by some HTABs. This area of research is not covered, and this could expose the data to critique in terms of clinical meaningfulness of the results.

Finally, the present research overall is focussed on providing PRO related evidence and value of enzalutamide, as reported out, one study after the other. This is a natural evolution of how pharmaceutical drug development is done and how clinical studies are reported out. However, in ideally the PRO and HRQoL analyses should follow a strategic, *a priori,* plan that prospectively inform the study design of appropriate integration of PRO instruments, both in terms of data collection time points as well as securing prostate cancer appropriate PRO instruments are used consistently in studies to allow comparative data across studies in the disease spectrum. This requires talking to the patients and conducting desk research early in the drug development process, in order to fully understand the key issues, the patient is facing with the disease. This is one of the short-comings and the reason for why I duly call out for this in my proposed Framework (Table 6.1).

6.4 Recommendations for Future Studies and Research

The field of PRO and QoL related research is evolving rapidly. This rapid evolution provides for many opportunities, both in terms of further standardization of methodologies, for instance in the field of handling missing data. It also provides for technological solutions for patient level data capturing that were not available a few years ago. One such field of technological advancement is the use of Multidimensional Computer Adaptive Testing (MCAT) to provide an iterative item level data capturing of the most relevant items (Morris et al., 2017). The MCAT builds on item response theory and computer adaptive testing. This methodology should at least be explored in future studies.

The item analysis should also be advanced in the enzalutamide, and other PCa studies, to provide further support to the existing conclusions and evidence. Indeed, further studies are

progressing (ARCHES; ClinicalTrials.gov.NCT02677896). Given the positive results of the previous papers, the study team has agreed to include the PRO analyses in the primary hypothesis testing hierarchy for this study and my team is preparing for such analyses. These analyses will provide both domain, - as well as item, -analyses. Future regulatory submissions of enzalutamide will be in a position to provide sufficient evidence to support additional label claims based on PRO and HRQoL data, and thus enable HTA submissions to solidify and enhance the patient experience sections. There are thus future opportunities for research in the field of PCa. Studies should secure PROs are included and that prospective plans are in place for analyses, both with the pre-specified algorithms, as well as item analyses.

Publishing further data and results need to cater for different audiences and different stakeholders. The HTABs need to understand how to interpret QoL data and how to translate this into benefits from a payer perspective. The treating physician is interested in using QoL as an additional measure of treatment effectiveness and benefits. The patients need to understand how the treatment may affect or improve his QoL. Publication plans must consider these different needs and publish in both clinical and other types of journals.

More concretely and as a next step and for the advancement of this research, I will aim to publish the framework as a follow-up publication to my first paper (Paper #1). I believe this framework may serve the industry well, if focusing on the educational aspects as to how to integrate PRO research and adapt to new requirements from the regulators (FDA, 2017, EMA, 2017). The industry is continuing to struggle internally with the need to secure support, funding and resources for conducting Outcomes Research and also phase challenges with reporting outcomes results in such a way that the evidence has impact and is useful for the patients.

Given the importance of my findings for enzalutamide, but also in terms of our internal structural shortcomings, I also believe that this research, and the learnings summarised in this thesis can serve me within my own organization and can be used for internal training of stakeholders.

6.5 Conclusion

In conclusion, the thesis has provided the support of the primary objective of the thesis. The PRO research provides structure for how PRO research should be implemented in drug development (Paper 1), as well as examples for how PRO analyses can provide over and above information as compared to standard PRO analyses, relevant for the patient (Paper 4, 5, 6 & 7). Lastly, it provides evidence linking PRO results with clinical outcomes and endpoints, such as OS (Paper 8). This can ultimately spare patients from unnecessary testing as PRO data can be used as predictive measures of outcome. All this provides additional information relevant to stakeholders and thus enhances the understanding of prostate cancer and how the outcome of patient care is improving with enzalutamide treatment. This is decreasing the uncertainty in decision making and thereby increasing the efficiency of health care in general.

As a conclusion of my work and the thesis:

The use of PROs in drug development enhances the understanding of prostate cancer progression as well as treatment impacts. PROs provide patient relevant information, reducing uncertainty in decision-making and thus help improve patient's care, while expediting access of new treatments to patients.

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